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SPECIFICATION

SUBSTITUTED PHENETHYLAMINE DERIVATIVES

5 TECHNICAL FIELD

This invention relates to substituted phenethylamine derivatives that function as a motilin receptor antagonist and that are useful as medicines.

10 BACKGROUND ART

Motilin, which is one of the gastrointestinal hormones, is a straight-chained peptide consisting of 22 amino acids and is well known to be responsible for regulating the motility of the gastrointestinal tract in animals including human. It has been reported that exogenously administered motilin causes contractions in humans and dogs that are similar to interdigestive migrating contractions, thus promoting gastric emptying (Itoh et al., Scand. J. Gastroenterol., 11, 93-110 (1976); Peeters et al., Gastroenterology 102, 97-101 (1992)). Hence, erythromycin derivatives which are an agonist of motilin are under development as an gastrointestinal tract motor activity enhancer (Satoh et al., J. Pharmacol. Exp. Therap., 271, 574-579 (1994); Lartey et al., J. Med. Chem., 38, 1793-1798 (1995); Drug of the Future, 19, 910-912 (1994)).

Peptide and polypeptide derivatives have been reported as antagonists of motilin receptors (Depoortere et

al., Eur. J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem. Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al., J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These derivatives are used as a pharmacological  
5 tool in the study of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

Motilin receptors had been known to occur principally  
10 in the duodenum but recently it has been shown that they also occur in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that motilin is involved not only in the motility of the  
15 upper part of the gastrointestinal tract but also in the motility of its lower part.

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome who were manifesting diarrhea and in patients with  
20 irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease. Other diseases that have been  
25 reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy

syndrome. The antagonists of motilin receptors have the potential to ameliorate irritable bowel syndrome and other diseased states accompanied by increased blood motilin levels.

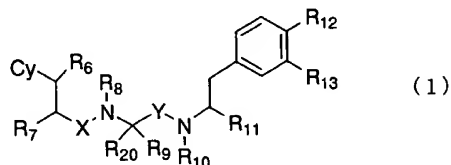
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# DISCLOSURE OF INVENTION

An object of the present invention is to provide substituted phenethylamine derivatives that function as an antagonist of motilin receptors and which are useful as medicines.

The present inventors conducted repeated intensive studies in an attempt to develop compounds having an outstanding motilin receptor antagonistic action. As a result, they found that substituted phenethylamine derivatives represented by Formula (1) were an excellent antagonist of motilin receptors. The present invention has been accomplished on the basis of this finding.

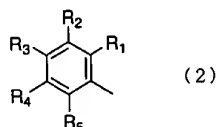
Thus, the present invention provides compounds of Formula (1):



20

wherein:

Cy is a group of Formula (2):



an optionally substituted heterocyclic ring, C<sub>3-7</sub>cycloalkyl or phenyl;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are hydrogen, halogen, hydroxy, amino, trifluoromethyl or nitrile and at least one of R<sub>1</sub>, R<sub>2</sub>,

5 R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> is halogen, trifluoromethyl or nitrile;

R<sub>6</sub> is hydrogen, optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl, amino or hydroxy;

R<sub>7</sub> is hydrogen, optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl, optionally substituted amino  
10 or hydroxy;

R<sub>8</sub> is hydrogen, methyl or ethyl;

R<sub>9</sub> is optionally substituted straight-chained or branched C<sub>1-6</sub>alkyl, optionally substituted straight-chained or branched C<sub>2-6</sub>alkenyl, optionally substituted straight-  
15 chained or branched C<sub>2-6</sub>alkynyl, C<sub>3-7</sub>cycloalkyl or optionally substituted phenyl;

R<sub>20</sub> is hydrogen or straight-chained or branched C<sub>1-3</sub>alkyl or R<sub>9</sub> and R<sub>20</sub> may together form C<sub>3-7</sub>cycloalkyl;

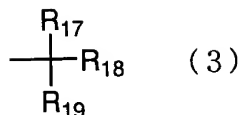
R<sub>10</sub> is hydrogen or straight-chained or branched  
20 C<sub>1-3</sub>alkyl;

R<sub>11</sub> is hydrogen, optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl, -CO-N(R<sub>14</sub>)R<sub>15</sub>, carboxyl or an optionally substituted heterocyclic ring;

R<sub>12</sub> is hydroxy or -OR<sub>16</sub>;

25 R<sub>13</sub> is hydrogen, straight-chained or branched C<sub>1-6</sub>alkyl, straight-chained or branched C<sub>2-6</sub>alkenyl, straight-chained or branched C<sub>2-6</sub>alkynyl or a group of Formula (3):





5  $R_{14}$  and  $R_{15}$ , which may be the same or different, are hydrogen, optionally substituted straight-chained or branched  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl, straight-chained or branched  $C_{1-4}$ alkyloxy, straight-chained or branched  $C_{1-4}$ alkylsulfonyl or a heterocyclic ring, or  $R_{14}$  and  $R_{15}$ , as -  $N(R_{14})R_{15}$ , form optionally substituted 3- to 7-membered cyclic amine;

$R_{16}$  is straight-chained  $C_{1-4}$ alkyl;

10  $R_{17}$  is hydrogen or methyl;

$R_{18}$  and  $R_{19}$  together form cycloalkyl or  $C_{3-7}$ cycloalkenyl;

$X$  is carbonyl or methylene;

$Y$  is carbonyl or methylene;

15 provided that

when Cy is 3-indolyl,

(i)  $R_{11}$  is an optionally substituted heterocyclic ring; or

(ii)  $R_6$  is hydrogen,  $R_7$  is amino,  $R_8$  is methyl,  $R_9$  is isopropyl,  $R_{20}$  is hydrogen,  $R_{10}$  is methyl,  $R_{11}$  is carbamoyl,  $R_{12}$  is hydroxy,  $R_{13}$  is tert-butyl,  $X$  is carbonyl and  $Y$  is carbonyl, and

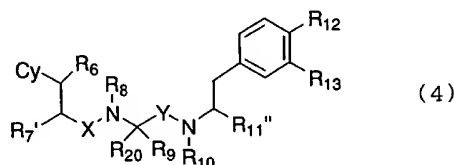
when Cy is cyclohexyl or phenyl,  $R_{11}$  is an optionally substituted heterocyclic ring,

25 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides a medicine

containing a compound of Formula (1) as an active ingredient. Further, the present invention provides a motilin receptor antagonist composition containing the compound. The present invention also provides a  
 5 gastrointestinal motility suppressor agent containing the compound as an active ingredient. Further, the present invention provides a therapeutic of hypermotilinemia containing the compound as an active ingredient.

The present invention also provides compounds of  
 10 Formula (4):



wherein

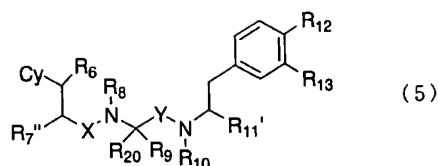
Cy, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, X and Y are as defined in claim 1;

15 R<sub>7</sub>' is hydrogen, straight-chained or branched C<sub>1-3</sub>alkyl optionally having at least one protected substituent, amino optionally having at least one protected substituent or protected hydroxy;

R<sub>11</sub>" is hydrogen, optionally substituted straight-  
 20 chained or branched C<sub>1-3</sub>alkyl, -CO-N(R<sub>14</sub>)R<sub>15</sub>, wherein R<sub>14</sub> and R<sub>15</sub> are as defined in claim 1, carboxyl, straight-chained or branched C<sub>1-3</sub>alkyl having protected amino or an optionally substituted heterocyclic ring;  
 or hydrates or pharmaceutically acceptable salts thereof.

25 The present invention also provides compounds of

Formula (5):



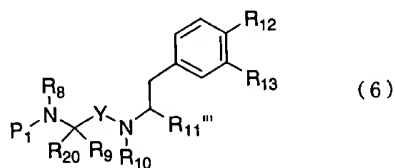
wherein:

Cy, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub>, X and Y are as defined  
 5 in claim 1;

R<sub>7</sub> is hydrogen, straight-chained or branched C<sub>1-3</sub>alkyl  
 optionally having at least one optionally protected  
 substituent, amino optionally having at least one  
 optionally protected substituent or optionally protected  
 10 hydroxy;

R<sub>11</sub>' is hydrogen, straight-chained or branched C<sub>1-3</sub>  
 alkyl optionally having at least one protected substituent,  
 -CO-N(R<sub>14</sub>)R<sub>15</sub> wherein R<sub>14</sub> and R<sub>15</sub> are as defined in claim 1,  
 carboxyl or an optionally substituted heterocyclic ring;  
 15 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of  
 Formula (6):



20 wherein:

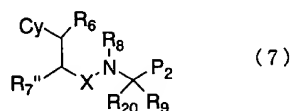
R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub>, R<sub>10</sub>, R<sub>12</sub>, R<sub>13</sub> and Y are as defined in claim  
 1;

P<sub>1</sub> is hydrogen or a protecting group of amine;

R<sub>11</sub>''' is hydrogen, optionally substituted straight-

chained or branched C<sub>1-3</sub>alkyl, -CO-N(R<sub>14</sub>)R<sub>15</sub> wherein R<sub>14</sub> and R<sub>15</sub> are as defined in claim 1, carboxyl, straight-chained or branched C<sub>1-3</sub>alkyl having protected amino or an optionally substituted heterocyclic ring;  
 5 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (7):



wherein:

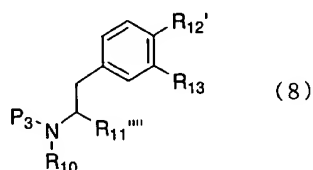
Cy, R<sub>6</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub> and X are as defined in claim 1;

R<sub>7</sub> is hydrogen, straight-chained or branched C<sub>1-3</sub>alkyl optionally having at least one optionally protected  
 15 substituent, amino optionally having at least one optionally protected substituent or optionally protected hydroxy;

P<sub>2</sub> is optionally protected carboxyl, formyl or methyl having a leaving group;

20 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (8)



wherein:

$R_{10}$  and  $R_{13}$  are as defined in claim 1;

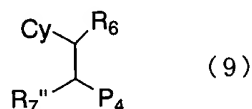
$P_3$  is hydrogen or a protecting group of amine;

$R_{11}$  is hydrogen, optionally substituted straight-  
5 chained or branched  $C_{1-3}$ alkyl,  $-CO-N(R_{14})R_{15}$  wherein  $R_{14}$  and  $R_{15}$   
are as defined in claim 1, carboxyl, straight-chained or  
branched  $C_{1-3}$ alkyl having protected amino or an optionally  
substituted heterocyclic ring;

$R_{12}$  is hydroxy or  $-OR_{16}$  wherein  $R_{16}$  is as defined in  
10 claim 1;  
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of  
Formula (9)

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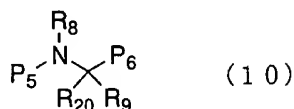
wherein:

$\text{Cy}$  and  $\text{R}_6$  are as defined in claim 1;

$\text{R}_7''$  is hydrogen, straight-chained or branched  $C_{1-3}$ alkyl  
20 optionally having at least one optionally protected  
substituent, amino optionally having at least one  
optionally protected substituent or optionally protected  
hydroxy;

$\text{P}_4$  is optionally protected carboxyl, formyl or methyl  
25 having a leaving group;  
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of  
Formula (10)



5 wherein:

$\text{R}_8$ ,  $\text{R}_9$  and  $\text{R}_{20}$  are as defined in claim 1;

$\text{P}_5$  is hydrogen or a protecting group of amine;

$\text{P}_6$  is optionally protected carboxyl, formyl or methyl  
having a leaving group;

10 or hydrates or pharmaceutically acceptable salts thereof.

In the definition of the compounds of Formula (1),  
halogen as  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  of Formula (2) as Cy is  
preferably fluorine or chlorine, with fluorine being more  
preferred. When at least 2 of  $\text{R}_1$  to  $\text{R}_5$  are halogen, they  
15 may be the same or different halogen, however it is  
preferable that they are the same. The number of halogen  
atoms is preferably 1 to 3 and more preferably 1 or 2.

Preferably, at least one of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  of  
Formula (2) as Cy is halogen, trifluoromethyl or nitrile  
20 and the others are independently hydrogen or hydroxy.

Preferably,  $\text{R}_3$  is halogen, trifluoromethyl or nitrile or  $\text{R}_2$   
and  $\text{R}_3$  are the same kind of halogen. Preferred compounds  
include those in which  $\text{R}_3$  is halogen and  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_4$  and  $\text{R}_5$   
are hydrogen; those in which  $\text{R}_2$  and  $\text{R}_3$  are the same halogen  
25 and  $\text{R}_1$ ,  $\text{R}_4$  and  $\text{R}_5$  are hydrogen; and those in which at least  
one of  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  is trifluoromethyl or nitrile  
and the others are hydrogen, halogen or hydroxy.

Preferred examples of the group of Formula (2) as Cy include 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl and 4-cyanophenyl, more preferably 4-fluorophenyl and 4-chlorophenyl, with 4-fluorophenyl being most preferred.

Preferred examples of the heterocyclic ring of the optionally substituted heterocyclic ring as Cy include aliphatic or aromatic 5- to 7-membered mono- or fused-rings containing at least one hetero atom selected from among N, S and O; specific examples include pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, indolyl, quinolinyl, benzoimidazolyl, benzodiazepinyl, benzofuryl, pyrrolidinyl, piperazinyl, piperidinyl and tetrahydroisoquinolinyl, with indolyl being preferred.

Exemplary substituents of the optionally substituted heterocyclic ring as Cy include hydroxy, methoxy, amino, methyl, ethyl, trifluoromethyl, carboxy, methoxycarbonyl and oxo. The heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different.

Preferably, the optionally substituted heterocyclic ring of Cy is 3-indolyl.

25            Preferably, the C<sub>3-7</sub>cycloalkyl as Cy is cyclopentyl or  
cyclohexyl.

While Cy has the definitions set forth above, Cy is preferably Formula (2) or an optionally substituted

heterocyclic ring, more preferably 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl and 3-indolyl, with 4-fluorophenyl being particularly preferred.

The alkyl of the optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>6</sub> is preferably methyl or ethyl.

10 Exemplary substituents of the optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>6</sub> include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

15 The optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>6</sub> is preferably methyl, ethyl, fluoromethyl or trifluoromethyl, with methyl being particularly preferred.

While R<sub>6</sub> has the definitions set forth above, R<sub>6</sub> is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>7</sub> is preferably methyl.

Exemplary substituents of the optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>7</sub> include halogen, hydroxy and amino, with hydroxy being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or



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branched C<sub>1-3</sub>alkyl as R<sub>7</sub> is preferably methyl or trifluoromethyl, with methyl being particularly preferred.

Exemplary substituents of the optionally substituted amino as R<sub>7</sub> include straight-chained or branched C<sub>1-3</sub>alkyl, with methyl and ethyl being preferred. The amino may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted amino as R<sub>7</sub> is preferably amino optionally substituted with one or more of the same or different kinds of straight-chained or branched C<sub>1-3</sub>alkyl; specific examples include amino, methylamino, dimethylamino and ethylamino, with amino and methylamino being particularly preferred.

While R<sub>7</sub> has the definitions set forth above, R<sub>7</sub> is preferably hydrogen or optionally substituted amino, with hydrogen, amino and methylamino being particularly preferred.

R<sub>8</sub> is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C<sub>1-6</sub>alkyl as R<sub>9</sub> is preferably straight-chained or branched C<sub>1-5</sub>alkyl, e.g., methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl and neopentyl.

Exemplary substituents of the optionally substituted straight-chained or branched C<sub>1-6</sub>alkyl as R<sub>9</sub> include substituted or unsubstituted phenyl (e.g., phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl), C<sub>3-7</sub>cycloalkyl, heterocyclic rings (e.g., pyrazyl, furyl, thienyl, pyrrolyl,

imidazolyl and quinolinyl) and halogen, with phenyl, cyclohexyl and thienyl being preferred.

The optionally substituted straight-chained or branched C<sub>1-6</sub>alkyl as R<sub>9</sub> is preferably methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, para-fluorobenzyl, 2-thienylmethyl, 3-indolylmethyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

The alkenyl of the optionally substituted straight-chained or branched C<sub>2-6</sub>alkenyl as R<sub>9</sub> is preferably vinyl, 2-propenyl, 2-propen-1-yl, 2-buten-1-yl or 2-isobuten-1-yl, with 2-propen-1-yl being more preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C<sub>2-6</sub>alkenyl as R<sub>9</sub> include phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

The optionally substituted straight-chained or branched C<sub>2-6</sub>alkenyl as R<sub>9</sub> is preferably 2-propen-1-yl.

The alkynyl of the optionally substituted straight-chained or branched C<sub>2-6</sub>alkynyl as R<sub>9</sub> is preferably ethynyl, propargyl or 2-butyn-1-yl, with 2-butyn-1-yl being preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C<sub>2-6</sub>alkynyl as R<sub>9</sub> include halogen, phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

The optionally substituted straight-chained or branched C<sub>2-6</sub>alkynyl as R<sub>9</sub> is preferably 2-butyn-1-yl.

The C<sub>3-7</sub>cycloalkyl as R<sub>9</sub> is preferably cyclopentyl or cyclohexyl.



halogen, carbamoyl, methanesulfonyl, ureide, guanidyl, N'-cyano-N"-methylguanidyl, sulfamoylamino, carbamoylmethylamino and methanesulfonylamino, with amino, hydroxy, carbamoyl, methanesulfonyl, ureide, sulfamoylamino, methanesulfonylamino and carbamoylmethylamino being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or branched C<sub>1-3</sub>alkyl as R<sub>11</sub> is preferably methyl, aminomethyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, guanidylmethyl, sulfamoylaminomethyl or methanesulfonylaminomethyl, with methyl, hydroxymethyl and methanesulfonylmethyl being more preferred.

The alkyl of the optionally substituted straight-  
15 chained or branched C<sub>1-4</sub>alkyl as R<sub>14</sub> and R<sub>15</sub> of -CO-N(R<sub>14</sub>)R<sub>15</sub> as  
R<sub>11</sub> is preferably methyl, ethyl, propyl, isopropyl, isobutyl,  
sec-butyl or tert-butyl, with methyl and ethyl being more  
preferred.

Exemplary substituents of the optionally substituted  
20 straight-chained or branched C<sub>1-4</sub>alkyl as R<sub>14</sub> and R<sub>15</sub> in -CO-  
N(R<sub>14</sub>)R<sub>15</sub> as R<sub>11</sub> include optionally substituted straight-  
chained or branched C<sub>1-3</sub>alkoxy (exemplary substituents of  
the optionally substituted straight-chained or branched  
C<sub>1-3</sub>alkoxy include hydroxy, amino, carboxyl and carbamoyl),  
25 hydroxy, amino, methylamino, dimethylamino, carbamoyl and  
methanesulfonyl, with hydroxy, methoxy and methanesulfonyl  
being preferred.

Examples of the optionally substituted straight-



carboxymethyl, alkoxycarbonylmethyl and methylsulfonyl.

The optionally substituted 3- to 7-membered cyclic amine as  $-N(R_{14})R_{15}$  of  $-CO-N(R_{14})R_{15}$  as  $R_{11}$  is preferably 4-carboxymethylpiperazine, 4-ethoxycarbonylpiperazine, 4-methylsulfonylpiperazine or morpholine.

The  $-CO-N(R_{14})R_{15}$  as  $R_{11}$  is preferably carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl and 4-methylsulfonyl-1-piperazinecarbonyl, with carbamoyl and ethylcarbamoyl being more preferred.

Examples of the heterocyclic ring of the optionally substituted heterocyclic ring as  $R_{11}$  include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O. Exemplary substituents of the heterocyclic ring include oxo, hydroxy, methyl, ethyl and trifluoromethyl; the heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different. Specific examples of the optionally substituted heterocyclic ring include furyl, thienyl, pyrrolyl, oxazolyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 4-pyrimidinon-2-yl, 6-methyl-4-pyrimidinon-2-yl

and imidazolidine-2,4-dione-5-yl, with 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidino-2-yl being preferred.

While  $R_{11}$  has the definitions set forth above,  $R_{11}$  is preferably methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidinon-2-yl, with carbamoyl and ethylcarbamoyl being more preferred.

The straight-chained  $C_{1-4}$ alkyl as  $R_{16}$  of  $-OR_{16}$  as  $R_{12}$  is preferably methyl.

$R_{12}$  is preferably hydroxy.

The straight-chained or branched  $C_{1-6}$ alkyl as  $R_{13}$  is preferably straight-chained or branched  $C_{2-5}$ alkyl, more preferably branched  $C_{3-5}$ alkyl, and most preferably tert-butyl.

The straight-chained or branched  $C_{2-6}$ alkenyl as  $R_{13}$  is preferably straight-chained or branched  $C_{3-5}$ alkenyl and more preferably branched  $C_{3-5}$ alkenyl.

The straight-chained or branched  $C_{2-6}$ alkynyl as  $R_{13}$  is

preferably straight-chained or branched C<sub>3-5</sub>alkynyl and more preferably branched C<sub>3-5</sub>alkynyl.

R<sub>17</sub> in Formula (3) as R<sub>13</sub> is preferably methyl.

The C<sub>3-7</sub>cycloalkyl formed by R<sub>18</sub> and R<sub>19</sub> in Formula (3)  
5 as R<sub>13</sub> is preferably C<sub>3-5</sub>cycloalkyl.

The C<sub>3-7</sub> cycloalkenyl formed by R<sub>18</sub> and R<sub>19</sub> in Formula (3) as R<sub>13</sub> is preferably C<sub>3-5</sub>cycloalkenyl.

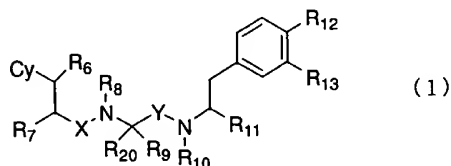
While R<sub>13</sub> has the definitions set forth above, R<sub>13</sub> is preferably isopropyl, tert-butyl, 1,1-dimethylpropyl and  
10 1,1-dimethyl-2-propenyl, with tert-butyl being more preferred.

X is preferably carbonyl or methylene.

Y is preferably carbonyl or methylene.

Examples of compounds of Formula (1)

15



wherein:

Cy, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, X and Y are as defined as above

20 include those compounds of which Cy is a group of Formula (2) in which at least one of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> is halogen and the others are hydrogen or hydroxy; R<sub>6</sub> is hydrogen or methyl; R<sub>7</sub> is hydrogen or optionally substituted amino; R<sub>8</sub> is hydrogen or methyl; R<sub>9</sub> is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl,  
25 phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or



cyclohexylmethyl; R<sub>20</sub> is hydrogen; R<sub>10</sub> is hydrogen or methyl; R<sub>11</sub> is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl; R<sub>12</sub> is hydroxy; R<sub>13</sub> is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl. More preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea, N-(2-(2-(2-amino-3-(4-fluorophenyl)propanoyl-N-methylamino)-3-methyl)butyrilamino)-3-(3-tert-butyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenyl)alanynoyl)methylamino]-3-methylbutanamide,

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- 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
- 5 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-
- 10 methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
- 15 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide, Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-
- 20 25

- tBu)-NH<sub>2</sub>, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET,
- 10 N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHcPr and Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHnPr Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHlPr.
- 25 Particularly preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, 2-((2-amino-3-(4-

5

fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid

methanesulfonylmethylethylamide and 2-(2-((2-amino-3-(4-

butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol.

10

Various protected functional groups are defined in Formulae

[illegible]

15

R<sub>7</sub>' include those which are known as useful protecting

benzyloxycarbonyl, t-butoxycarbonyl, 9-

20

trimethylsilyl, t-butyldimethylsilyl, benzyl,

of the protecting groups of the protected substituent of

25

benzyloxycarbonyl, t-butoxycarbonyl, 9-

acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl,



known as useful protecting groups of amino; specific  
examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-  
fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl,  
acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl,  
5 trimethylsilyl, t-butyldimethylsilyl, benzyl and  
benzyloxymethyl. Examples of the protecting groups of the  
optionally protected hydroxy as R<sub>7</sub> include those which are  
known as useful protecting groups of hydroxy; specific  
examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-  
10 fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl,  
acetyl, trifluoroacetyl, trimethylsilyl, t-  
butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and  
tetrahydropyranyl.

Examples of the protecting groups of the protected  
15 substituent of the straight-chained or branched C<sub>1-3</sub>alkyl as  
R<sub>11</sub> include those which are known as useful protecting  
groups of amino or hydroxy; specific examples are  
benzyloxycarbonyl, t-butoxycarbonyl, 9-  
fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl,  
20 acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl,  
trimethylsilyl, t-butyldimethylsilyl, benzyl,  
benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of amine as P<sub>1</sub>  
include those which are known as useful protecting groups  
25 of amino; specific examples are benzyloxycarbonyl, t-  
butoxycarbonyl, 9-fluorenylmethyloxycarbonyl,  
allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl,  
benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched  $C_{1-3}$ alkyl as  $R_{11}$ ''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

10 Examples of the protecting groups of the optionally protected carboxyl as  $P_2$  include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

15 Examples of the protecting groups of amine as  $P_3$  include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, 20 benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched  $C_{1-3}$ alkyl as  $R_{11}$ ''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P<sub>4</sub> include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Examples of the protecting groups of amine as P<sub>5</sub> include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P<sub>6</sub> include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.



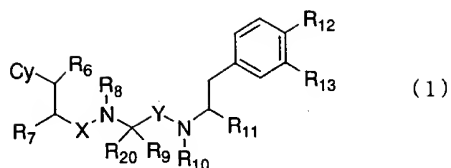
The compounds of the present invention can also be obtained as hydrates.

The subject application claims priority on the basis of Japanese Patent Application Nos. 11-20523 and 11-283163  
5 all disclosures in their specification shall be incorporated herein by reference.

On the pages that follow, the present invention is described more specifically and the amino acids that constitute peptides, the amino acids protected by  
10 protecting groups, the protecting groups, reagents and solvents are represented by the following abbreviations:  
Val: valine, Phe: phenylalanine, Tyr: tyrosine, Z: benzyloxycarbonyl, Boc: tert-butoxycarbonyl, CMPI: 2-chloro-1-methylpyridinium iodide, PyCIU: chloro-N,N,N',N'-  
15 bis(tetramethylene)formamidinium hexafluorophosphate, DIC: N,N'-diisopropylcarbodiimide, HOBT: 1-hydroxylbenzotriazole monohydrate, NMM: N-methylmorpholine, TEA: triethylamine, DIEA: diisopropylethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran, DMF: N,N-dimethylformamide, CH:  
20 chloroform, MC: methylene chloride, M: methanol, N: concentrated aqueous ammonia, EA: ethyl acetate, H and nHx: n-hexane and ACT: acetone.

#### BEST MODE FOR CARRYING OUT THE INVENTION

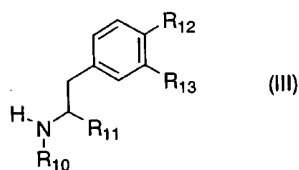
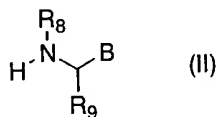
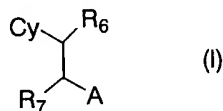
25 The compounds of Formula (1)



wherein Cy, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, R<sub>20</sub>, R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, X and Y are as defined above

- 5 can basically be produced by binding Compound (I), Compound (II) and Compound (III), which are represented by the following formulae and in which functional groups other than those involved in bond formation are protected as required:

10



- 15 A and B in Formulae (I) to (III) are functional groups which can form a bond by the reaction with amino; specific examples are carboxyl, formyl, halomethylene of which halogen is chlorine, bromine or iodine, and sulfonyloxymethylene of which sulfonyl is methanesulfonyl, trifluoromethanesulfonyl, paratoluenesulfonyl and the like.
- 20 R<sub>1</sub> to R<sub>10</sub>, R<sub>12</sub> and R<sub>13</sub> are as defined above, provided that

when they are reactive groups such as amino, hydroxy or  
carboxyl, they are protected by normally used appropriate  
protecting groups, if desired. R<sub>11</sub> is as defined above or  
is a functional group which is convertible to one of the  
5 above defined groups.

The compounds of Formula (1) may be produced by first  
binding Compound (II) and Compound (III), optionally  
followed by deprotection, and then binding the resultant  
compound with Compound (I), optionally followed by  
10 deprotection or conversion of the functional group(s).  
Alternatively, the compound of Formula (1) may be produced  
by first binding Compound (I) and Compound (II), optionally  
followed by deprotection, and then binding the resultant  
compound with Compound (III), optionally followed by  
15 deprotection or conversion of the functional group(s).

The compounds of the present invention may be  
produced by either the solid-phase process or the liquid-  
phase process. In the production by the solid-phase  
process, an automatic organic synthesizer can be used but  
20 it may be replaced by the manual procedure.

Almost all amino acids that are used for the  
production of the compounds of the present invention are  
commercially available and readily purchasable. Those  
which are not commercially available can be produced by  
25 well-known established methods such as the Strecker  
synthesis, the Bucherer method, the acetamido malonic ester  
method, the method of alkylating an amino group protected  
glycine ester and the Z- $\alpha$ -phosphonoglycine trimethylester

method.

Compound (I), if it has a functional group such as amino and hydroxy, with the functional group being protected, is carboxylic acid (A is  $-\text{CO}_2\text{H}$ ), aldehyde (A is  $-\text{CHO}$ ), alkylhalide (A is  $-\text{CH}_2\text{-Hal}$ ), sulfonate (A is  $-\text{CH}_2\text{-OSO}_2\text{R}$ ) or the like. In this case, bond can be formed by reacting A of Compound (I) with the amino group of Compound (II).

Compound (II) can, in almost all cases, be derived from an  $\alpha$ -amino acid and B is carboxyl ( $-\text{CO}_2\text{H}$ ), formyl ( $-\text{CHO}$ ), halomethyl ( $-\text{CH}_2\text{-Hal}$ ), sulfonyloxymethyl ( $\text{RSO}_2\text{O-CH}_2\text{-}$ ) or the like. The amino group of Compound (II) is reacted with A of Compound (I) to form bond and B of Compound (II) is reacted with the amino group of Compound (III) to form bond.

Compound (III) is an ethylamine derivative and can be generally derived from an amino acid. The amino group of Compound (III) is reacted with B of Compound (II) to form bond.

When A or B is carboxyl, various methods known in peptide synthesis may be used to activate the carboxyl for condensation with the amino group and such methods include the use of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), the use of PyCIU, the use of bromo tripyrrolidino phosphonium hexafluorophosphate (PyBrop), the use of chlorotripyrrolidino phosphonium hexafluorophosphate (PyClop), the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-

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tetramethyluronium hexafluorophosphate (HATU), the use of  
DIC, the use of N-ethyl-N'-3-dimethylaminopropyl  
carbodiimide (WSCl), the use of dicyclohexyl carbodiimide  
(DCC), the use of diphenylphosphorylazide (DPPA), the use  
5 of CMPI, the use of 2-bromo-1-methylpyridinium iodide  
(BMPI), the combination of one of these reagents with HOBT  
or N-hydroxysuccinimide (HONSu), the mixed acid anhydride  
method using isobutyl chloroformate or the like, the method  
of changing the carboxyl group to a pentafluorophenyl ester  
10 (OPfp), a p-nitrophenyl ester (ONP) or an N-  
hydroxysuccinimide ester (OSu), and the combination of one  
of these methods with HOBT. If necessary, a base such as  
TEA, DIEA, NMM or 4-dimethylaminopyridine (DMAP) may be  
added to accelerate the reaction.

15       When A or B is formyl, bond can be formed by  
conventional reductive bond forming reaction with amino  
group. When A or B is halomethylene or  
sulfonyloxymethylene, bond can be formed by substitution  
reaction with amino group.

20       The compounds of the present invention can also be  
produced by applying the specific methods of production to  
be described in the following Examples.

On the pages that follow, the production of the  
compounds of the invention is described more specifically  
25 by reference to Examples, to which the invention is by no  
means limited.

In order to demonstrate the utility of the compounds  
of the invention, typical examples of them were subjected

to pharmacological tests on the motilin receptor  
antagonistic action and the results are described under  
Test Examples. The chemical structural formulae or  
chemical names of the compounds produced in Examples are  
5 set forth in Tables A-1 to A-10 and Tables B-1 to B-18.

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Table A-1

Example No.	Structural formula or chemical name
1	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
2	Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
3	Phe(3,4-F <sub>2</sub> )-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
4	Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
5	Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
6	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHSO <sub>2</sub> Me TFAsalt
7	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe
8	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric 2-(3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide
9	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea
10	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine
11	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine
12	2-(2-(2-amino-3-(4-fluorophenyl)propanoyl-N-methylamino)-3-methyl)butyrilamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylsulfamide

Table A-2

Example No.	Structural formula or chemical name
13	2-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylaminoacetamide
14	N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminoethyl)-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
15	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide
16	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide
17	2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butylamino)-3-(3-tBu-4-hydroxyphenyl)propanol
18	(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone
19	2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone
20	5-(1-(2-((2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
21	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide



Table 1		Table 2		Table 3		Table 4		Table 5		Table 6		Table 7		Table 8		Table 9		Table 10		Table 11		Table 12		Table 13		Table 14		Table 15		Table 16		Table 17		Table 18		Table 19		Table 20		Table 21		Table 22		Table 23		Table 24		Table 25		Table 26		Table 27		Table 28		Table 29		Table 30		Table 31		Table 32		Table 33		Table 34		Table 35		Table 36		Table 37		Table 38		Table 39		Table 40		Table 41		Table 42		Table 43		Table 44		Table 45		Table 46		Table 47		Table 48		Table 49		Table 50		Table 51		Table 52		Table 53		Table 54		Table 55		Table 56		Table 57		Table 58		Table 59		Table 60		Table 61		Table 62		Table 63		Table 64		Table 65		Table 66		Table 67		Table 68		Table 69		Table 70		Table 71		Table 72		Table 73		Table 74		Table 75		Table 76		Table 77		Table 78		Table 79		Table 80		Table 81		Table 82		Table 83		Table 84		Table 85		Table 86		Table 87		Table 88		Table 89		Table 90		Table 91		Table 92		Table 93		Table 94		Table 95		Table 96		Table 97		Table 98		Table 99		Table 100		Table 101		Table 102		Table 103		Table 104		Table 105		Table 106		Table 107		Table 108		Table 109		Table 110		Table 111		Table 112		Table 113		Table 114		Table 115		Table 116		Table 117		Table 118		Table 119		Table 120		Table 121		Table 122		Table 123		Table 124		Table 125		Table 126		Table 127		Table 128		Table 129		Table 130		Table 131		Table 132		Table 133		Table 134		Table 135		Table 136		Table 137		Table 138		Table 139		Table 140		Table 141		Table 142		Table 143		Table 144		Table 145		Table 146		Table 147		Table 148		Table 149		Table 150		Table 151		Table 152		Table 153		Table 154		Table 155		Table 156		Table 157		Table 158		Table 159		Table 160		Table 161		Table 162		Table 163		Table 164		Table 165		Table 166		Table 167		Table 168		Table 169		Table 170		Table 171		Table 172		Table 173		Table 174		Table 175		Table 176		Table 177		Table 178		Table 179		Table 180		Table 181		Table 182		Table 183		Table 184		Table 185		Table 186		Table 187		Table 188		Table 189		Table 190		Table 191		Table 192		Table 193		Table 194		Table 195		Table 196		Table 197		Table 198		Table 199		Table 200		Table 201		Table 202		Table 203		Table 204		Table 205		Table 206		Table 207		Table 208		Table 209		Table 210		Table 211		Table 212		Table 213		Table 214		Table 215		Table 216		Table 217		Table 218		Table 219		Table 220		Table 221		Table 222		Table 223		Table 224		Table 225		Table 226		Table 227		Table 228		Table 229		Table 230		Table 231		Table 232		Table 233		Table 234		Table 235		Table 236		Table 237		Table 238		Table 239		Table 240		Table 241		Table 242		Table 243		Table 244		Table 245		Table 246		Table 247		Table 248		Table 249		Table 250		Table 251		Table 252		Table 253		Table 254		Table 255		Table 256		Table 257		Table 258		Table 259		Table 260		Table 261		Table 262		Table 263		Table 264		Table 265		Table 266		Table 267		Table 268		Table 269		Table 270		Table 271		Table 272		Table 273		Table 274		Table 275		Table 276		Table 277		Table 278		Table 279		Table 280		Table 281		Table 282		Table 283		Table 284		Table 285		Table 286		Table 287		Table 288		Table 289		Table 290		Table 291		Table 292		Table 293		Table 294		Table 295		Table 296		Table 297		Table 298		Table 299		Table 300	
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Table A-4

Example No.	Structural formula or chemical name
26	Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
27	Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
28	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH <sub>2</sub>
29	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH <sub>2</sub>
30	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH <sub>2</sub>
31	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
32	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
33	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
34	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
35	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
36	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
37	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
38	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
39	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub>
40	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub>
41	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub>
42	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
43	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
44	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
45	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH <sub>2</sub>
46	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH <sub>2</sub>
47	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH <sub>2</sub>
48	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe
49	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe
50	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

Table A-5

Example No.	Structural formula or chemical name
51	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
52	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH <sub>2</sub>
53	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH <sub>2</sub>
54	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe
55	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
56	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
57	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub>
58	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH <sub>2</sub>
59	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH <sub>2</sub>
60	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe
61	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
62	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
63	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu
64	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH <sub>2</sub> SO <sub>2</sub> CH <sub>3</sub>
65	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
66	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
67	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
68	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide
69	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide
70	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

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Table A-6

Example No.	Structural formula or chemical name
71	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
72	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
73	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
74	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
75	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
76	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
77	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-N,3-dimethylbutanamide
78	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Table A-7

Example No.	Structural formula or chemical name
101	Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH <sub>2</sub> t
102	N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH <sub>2</sub> t
103	N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH <sub>2</sub> t
104	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> t
105	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> t
106	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> t
107	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
108	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
109	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
110	Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH <sub>2</sub> t
111	N-Me-Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH <sub>2</sub> t
112	N-Et -Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH <sub>2</sub> t
113	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> t
114	N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> t
115	N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NH <sub>2</sub> t
116	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
117	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
118	N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH <sub>2</sub> t
119	Phe(4-F)-N-Me-Val- Tyr(3-t Bu)-NH-n-Pr
120	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr
121	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr
122	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH <sub>2</sub> OH
123	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH <sub>2</sub> OH
124	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH <sub>2</sub> OH
125	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH <sub>2</sub> OH

Table A-8

Example No.	Structural formula or chemical name
126	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH <sub>2</sub> OH
127	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH <sub>2</sub> OH
128	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH <sub>2</sub> OH
129	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH <sub>2</sub> OH
130	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH <sub>2</sub> OH
131	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH <sub>2</sub> OH
132	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH <sub>2</sub> OH
133	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-morpholin-4-yl)-2-oxoethyl)-3-methyl-N-methylbutanamide
134	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide
135	ethyl 2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanol)piperazinyl]acetate
136	2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanol)piperazinyl]acetic acid
137	Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH <sub>2</sub>
138	Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
139	Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
140	Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH <sub>2</sub>

Figure 1 consists of 12 histograms, labeled (a) through (l), each representing a different disease. The x-axis for all histograms is 'Number of contacts' and the y-axis is 'Frequency'. The data is as follows:

Disease	Number of contacts	Frequency
a) HIV	0	10
	1	15
	2	10
	3	5
b) Hepatitis B	0	10
	1	15
	2	10
	3	5
c) Hepatitis C	0	10
	1	15
	2	10
	3	5
d) Tuberculosis	0	10
	1	15
	2	10
	3	5
e) Measles	0	10
	1	15
	2	10
	3	5
f) Polio	0	10
	1	15
	2	10
	3	5
g) Malaria	0	10
	1	15
	2	10
	3	5
h) Dengue	0	10
	1	15
	2	10
	3	5
i) Typhoid	0	10
	1	15
	2	10
	3	5
j) Cholera	0	10
	1	15
	2	10
	3	5
k) Pertussis	0	10
	1	15
	2	10
	3	5
l) Tetanus	0	10
	1	15
	2	10
	3	5

Example No.	Structural formula or chemical name
141	Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
142	Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
143	Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
144	Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
145	Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
146	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide
147	(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide
148	Phe(4-F)-N-Me-Leu( $\gamma$ -Me)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
149	Phe(4-F)-N-Me-D-Leu( $\gamma$ -Me)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
150	Phe(4-F)-N-Me-Ala( $\beta$ -CF <sub>3</sub> )-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
151	Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
152	Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
153	Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
154	Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
155	Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
156	Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
157	Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
158	Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
159	Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
160	Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
161	Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
162	Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
163	Phe(4-F)-N-Me-Ala( $\beta$ -2-thienyl)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>

Table A-10

Example No.	Structural formula or chemical name
164	Phe(4-F)-N-Me-D-Ala( $\beta$ -2-thienyl)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
165	Phe(4-F)-N-Me-Ala( $\beta$ -c-Pr)-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
166	Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
167	Phe(4-F)-N-Me- $\alpha$ -Me-Phe-Tyr(3-tBu)-NH <sub>2</sub>
168	Phe(4-F)-N-Me- $\alpha$ -Me-Phe-Tyr(3-tBu)-NH <sub>2</sub>
169	Phe(4-F)-N-Me- $\alpha$ -Me-Leu-Tyr(3-tBu)-NH <sub>2</sub>
170	Phe(4-F)-N-Me- $\alpha$ -Me-D-Abu-Tyr(3-tBu)-NH <sub>2</sub>
171	Phe(4-F)-N-Me- $\alpha$ -Me-D-Val-Tyr(3-tBu)-NH <sub>2</sub>
172	(2S)-N-[(N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
173	(2S)-N-[(N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
174	Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH <sub>2</sub>
175	Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
176	Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
177	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
178	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
179	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino]-3-methyl-N-methylbutanamide
180	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
181	Ala( $\beta$ -4-pyridyl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
182	Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>
183	Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub>



09890219 72101  
T027 6206860

Table B-1

Example No.	Structural formula
1	
2	
3	
4	
5	

**Abstract**

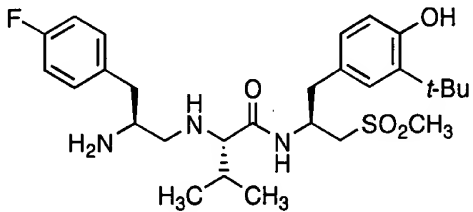
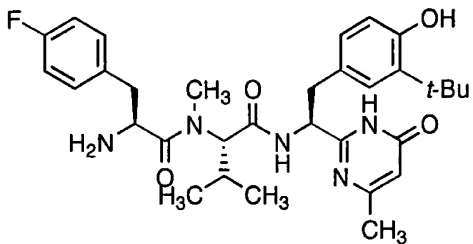
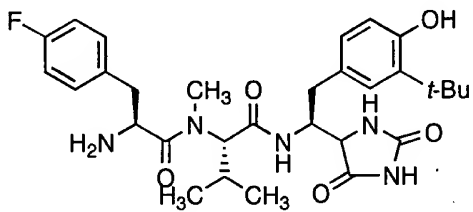
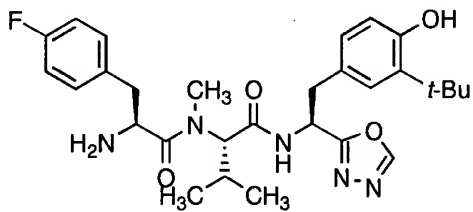
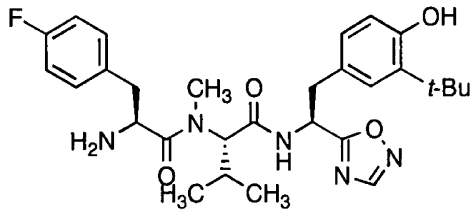
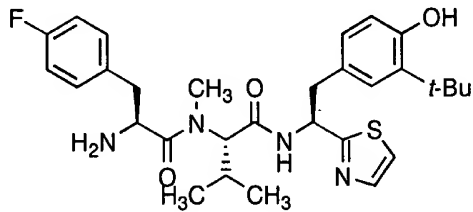
- 46 -

0000019-12101

Table B-3

Example No.	Structural formula
12	
13	
14	
15	
16	
17	

Table B-4

Example No.	Structural formula
18	
19	
20	
21	
22	
23	

098902219 121201

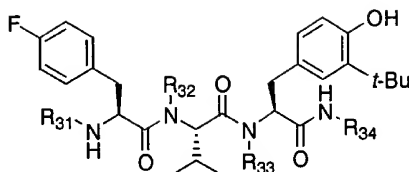
Table B-5

Example No.	Structural formula
24	
25	

5 Table B-6

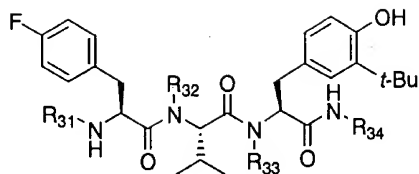
Example No.	Structural formula
26	
27	

Table B-7



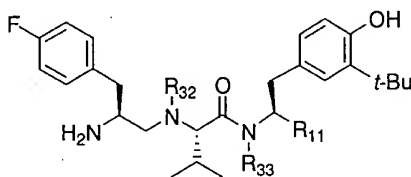
Example No.	R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>	Example No.	R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>
28	H	Me	H	H	54	H	Et	Me	Me
29	Me	Me	H	H	55	Me	Et	Me	Me
30	Et	Me	H	H	56	Et	Et	Me	Me
31	H	Me	H	Me	57	H	Et	Et	H
32	Me	Me	H	Me	58	Me	Et	Et	H
33	Et	Me	H	Me	59	Et	Et	Et	H
34	Me	Me	Me	H	60	H	Et	Et	Me
35	Et	Me	Me	H	61	Me	Et	Et	Me
36	H	Me	Me	Me	62	Et	Et	Et	Me
37	Me	Me	Me	Me	101	H	Me	H	Et
38	Et	Me	Me	Me	102	Me	Me	H	Et
39	H	Me	Et	H	103	Et	Me	H	Et
40	Me	Me	Et	H	122	H	Me	H	CH <sub>2</sub> OH
41	Et	Me	Et	H	123	Me	Me	H	CH <sub>2</sub> OH
42	H	Me	Et	Me	124	Et	Me	H	CH <sub>2</sub> OH
43	Me	Me	Et	Me	104	H	Me	Me	Et
44	Et	Me	Et	Me	105	Me	Me	Me	Et
45	H	Et	H	H	106	Et	Me	Me	Et
46	Me	Et	H	H	132	H	Me	Me	CH <sub>2</sub> OH
47	Et	Et	H	H	125	Me	Me	Me	CH <sub>2</sub> OH
48	H	Et	H	Me	126	Et	Me	Me	CH <sub>2</sub> OH
49	Me	Et	H	Me	107	H	Me	Et	Et
50	Et	Et	H	Me	108	Me	Me	Et	Et
51	H	Et	Me	H	109	Et	Me	Et	Et
52	Me	Et	Me	H	127	H	Me	Et	CH <sub>2</sub> OH
53	Et	Et	Me	H	128	Me	Me	Et	CH <sub>2</sub> OH
					129	Et	Me	Et	CH <sub>2</sub> OH

Table B-8



Example No.	R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>
110	H	Et	H	Et
111	Me	Et	H	Et
112	Et	Et	H	Et
113	H	Et	Me	Et
114	Me	Et	Me	Et
115	Et	Et	Me	Et
116	H	Et	Et	Et
117	Me	Et	Et	Et
118	Et	Et	Et	Et
130	H	Et	Et	CH <sub>2</sub> OH
131	Me	Et	Et	CH <sub>2</sub> OH
121	H	Me	Me	cPr
119	H	Me	H	nPr
120	H	Me	H	iPr
137	H	Me	nPr	H
63	H	Me	H	tBu
64	H	Me	Me	CH <sub>2</sub> SO <sub>2</sub> CH <sub>3</sub>

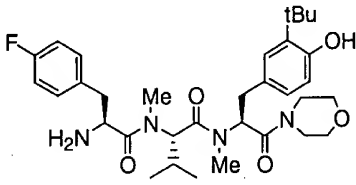
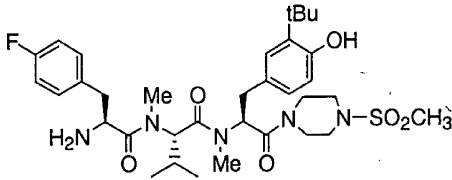
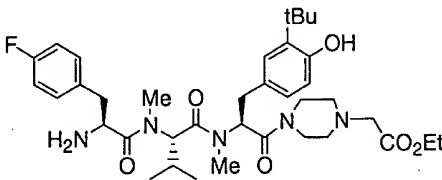
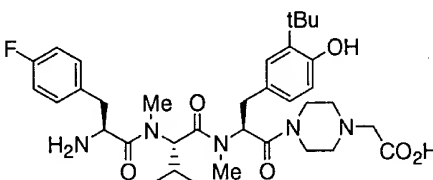
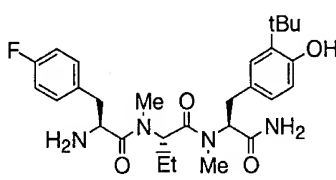
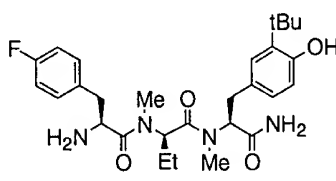
Table B-9



5

Example No.	R <sub>32</sub>	R <sub>33</sub>	R <sub>11</sub>	Example No.	R <sub>32</sub>	R <sub>33</sub>	R <sub>11</sub>
65	H	Me	CONH <sub>2</sub>	72	Me	Me	Me
66	Me	Me	CONH <sub>2</sub>	73	Ac	Me	Me
67	Ac	Me	CONH <sub>2</sub>	74	H	H	Me
68	H	Et	CONH <sub>2</sub>	75	Me	H	Me
69	H	H	CH <sub>2</sub> OH	76	Ac	H	Me
70	Me	H	CH <sub>2</sub> OH	77	Me	Me	CH <sub>2</sub> OH
71	H	Me	Me	78	Me	H	CH <sub>2</sub> NH <sub>2</sub>

Table B-10

Example No.	Structural formula
133	
134	
135	
136	
138	
139	



0950219.121201

Table B-11

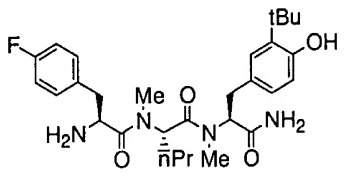
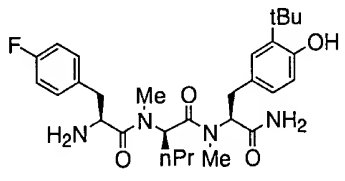
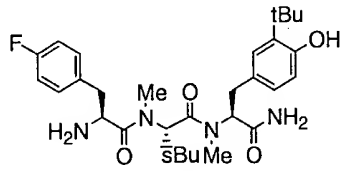
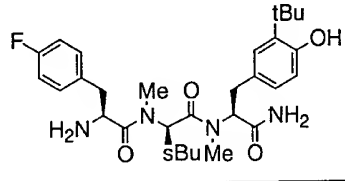
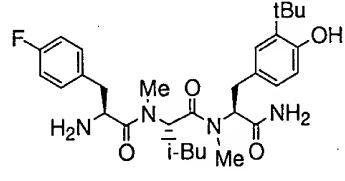
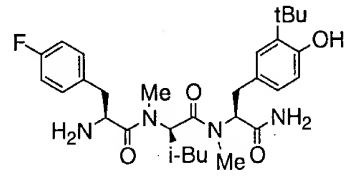
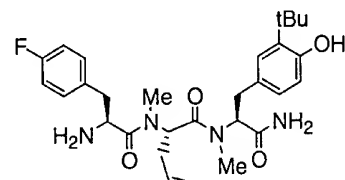
Example No.	Structural formula
140	
141	
142	
143	
144	
145	
146	

Table B-12

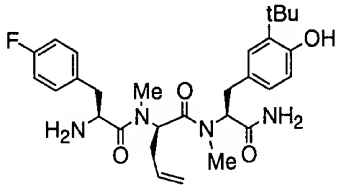
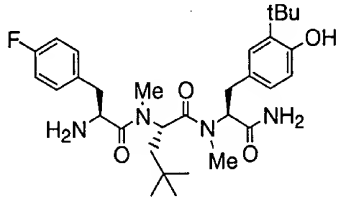
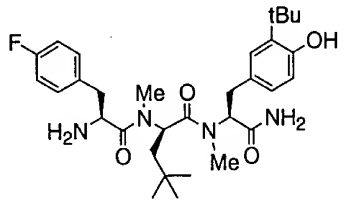
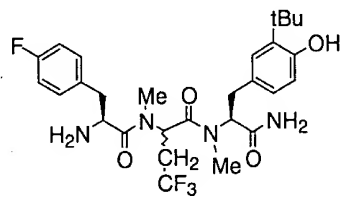
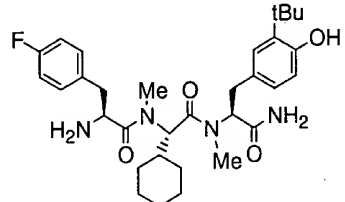
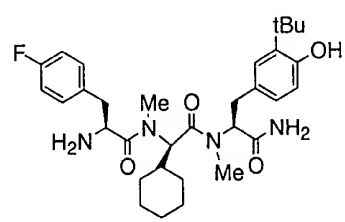
Example No.	Structural formula
147	
148	
149	
150A, 150B	
151	
152	

Table B-13

Example No.	Structural formula
153	
154	
155	
156	
157	

00000219 121204

Table B-14

Example No.	Structural formula
158	
159	
160	
161	
162	

[illegible]

- 57 -

Table B-16

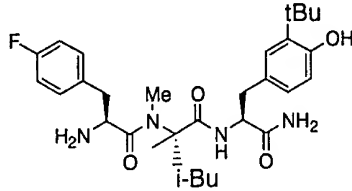
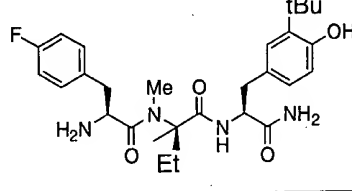
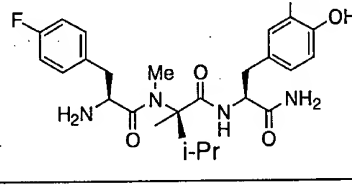
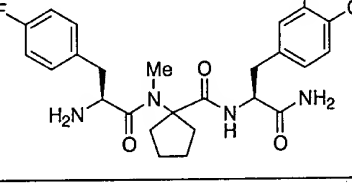
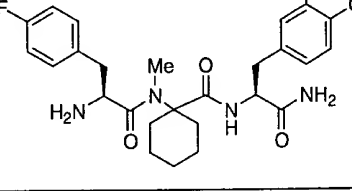
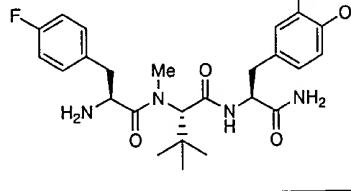
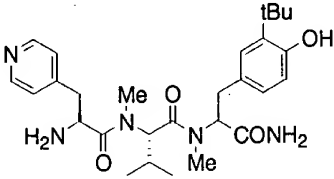
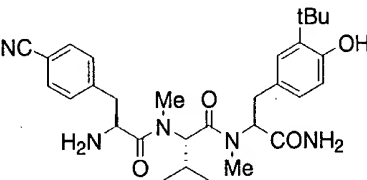
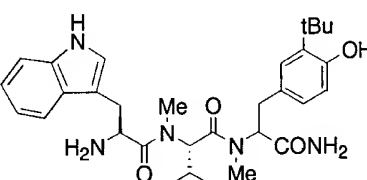
Example No.	Structural formula
169	
170	
171	
172	
173	
174	

Table B-17

Example No.	Structural formula
175	
176	
177A, 177B	
178A, 178B	
179A, 179B	
180A, 180B	

Table B-18

Example No.	Structural formula
181	
182	
183	

000001 121201



000001 121301  
102121 61200000

In the following Examples, Merck Silica gel 60 (0.063-0.200 mm) or Merck Silica gel 60 (0.040-0.063 mm) was used for silica gel column chromatography unless otherwise stated.

- 5 In the following examples, mass spectra (MA) and <sup>1</sup>H-NMR were taken by the following equipment:  
MA (EI-MS): SHIMADZU GCMS-QP5050A or SHIMADZU GCMS-QP1000.  
MA (ESI-MS): Extrel ELQ400  
MA (FAB-MS): JASCO 70-250SEQ

- 10 <sup>1</sup>H-NMR: JEOL JNM-EX-270 (270 MHz) or Bruker ARX300 (300 MHz)

- Reaction conditions, data from the equipment, yielded amount and the like of Example 28 onward were shown in Tables in which "Reaction time" means stirring time and  
15 "Column sol." means the eluting solvent for silica gel column chromatography.

In the following Examples, the retention time (min.) on HPLC is measured under the following conditions:

- Apparatus: HITACHI L-6300 or Young Lin M930  
20 Column:  $\mu$ BONDASPHERE 5 $\mu$  C18 100A (3.9 $\times$ 150 mm)  
Detecting conditions: linear gradient of B (10-80%) using A (0.1% TFA/distilled water) and B (0.1% TFA/acetonitrile), 35 min., flow of rate 1 ml/min, detected at 280 nm (UV).

- 25 Example 1

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of Tyr-OMe $\cdot$ HCl (500 g, 2.16 mol) in



<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz),  
3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s),  
5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz),  
6.78(1H,dd,J=7.9,2.0Hz), 6.95(1H,d,J=2.0Hz), 7.26-  
5 7.41(5H,m)

(3) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

A solution of Z-Tyr(3-tBu)-OMe (1.0 g, 2.60 mmol),  
benzyl bromide (0.56 ml, 4.68 mmol) and potassium carbonate  
(1.08 g, 7.79 mmol) in DMSO (5 ml) was stirred overnight.

10 The resulting mixture was mixed with a saturated aqueous  
ammonium chloride solution, extracted with ethyl acetate.  
The organic layer was washed with water and then saturated  
brine, dried over anhydrous magnesium sulfate and  
evaporated to remove the solvent under reduced pressure;  
15 the thus obtained residue was subjected to silica gel  
column chromatography (developing solvent: ethyl acetate:n-  
hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g,  
99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36(9H,s), 3.05(2H,d,J=5.6Hz), 3.71(3H,s),  
20 4.60-4.68(1H,m), 5.06(2H,s), 5.09(2H,s),  
5.24(1H,brd,J=8.3Hz), 6.82(1H,d,J=8.5Hz),  
6.88(1H,dd,J=8.5,1.8Hz), 7.00(1H,d,J=1.8Hz), 7.27-  
7.50(10H,m)

(4) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH<sub>2</sub>

25 To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g,  
2.60 mmol) in 1,4-dioxane (30 ml), a 2N aqueous sodium  
hydroxide solution (3 ml) was added and stirred for 2 hours.  
The resulting mixture was mixed with water and washed with

ethyl acetate; the aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent  
5 under reduced pressure, giving crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g).

To a solution of the thus obtained crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g) in THF (7 ml), under cooling with ice, methyl iodide (1.3 ml, 20.8 mmol) was added and then  
10 sodium hydride (60% in oil, 312 mg, 7.8 mmol) was added slowly, followed by stirring for 21 hours at room temperature. The resulting mixture was mixed with water, rendered acidic by the addition of dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was  
15 washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g).

To a solution of the thus obtained crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g) in THF (25 ml), under  
20 cooling with ice, ethyl chloroformate (0.27 ml, 2.86 mmol) and NMM (0.31 ml, 2.86 mmol) were added in that order. The mixture was stirred for 15 min. and further stirred for another 15 min. while bubbling gaseous ammonia therein.  
25 The resultant mixture was left standing at room temperature, diluted with ethyl acetate and washed with water and then saturated brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH<sub>2</sub> (1.08 g, 88%, in 3 steps).

5 <sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.37(9H,s), 2.87(3H,s), 2.86-2.99(1H,m), 3.21-3.35(1H,m), 4.73-4.95(1H,m), 5.06(2H,s), 5.09(2H,s), 5.67,5.83 and 6.13(3/2H,brs), 6.78-7.47(27/2H,m)

(5) Synthesis of N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH<sub>2</sub> (1.08 g, 2.28 mmol) in methanol (20 ml), 10% palladium/carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was  
15 subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.55 g, 96%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.40(9H,s), 2.31(3H,s), 2.63(1H,dd,J=14.7,10.7Hz), 3.10-3.19(2H,m), 5.24(1H,brs),  
20 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=7.9,1.8Hz), 7.05(1H,brs), 7.10(1H,d,J=1.8Hz)

(6) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Z-N-Me-Val-OH (700 mg, 2.64 mmol), N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.55 g, 2.20 mmol) and CMPI (674 mg  
25 2.64 mmol) in THF (22 ml), under cooling with ice, TEA (0.61 ml) was added and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed

with saturated brine, dried over sodium sulfate and  
evaporated to remove the solvent under reduced pressure;  
the thus obtained residue was subjected to silica gel  
column chromatography (developing solvent: ethyl acetate:n-  
5 hexane = 3:2) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.98  
g, 90%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(four rotamers) δ 0.07, 0.32, 0.63, 0.74,  
0.79, 0.81, 0.84 and 0.89(6H,d,J=6.3-6.6Hz), 1.30, 1.33,  
1.37 and 1.39(9H,s), 2.13-2.33(1H,m), 2.34, 2.41, 2.78,  
10 2.87 and 2.98(6H,s), 2.79-3.22(2H,m), 4.40 and  
4.32(1H,d,J=10.6Hz), 4.60-5.43(5H,m), 5.96(1H,brs),  
6.23-7.12(3H,m), 7.26-7.47(5H,m)

(7) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (Intermediate  
I-b3 in the following Tables)

15 A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.98 g,  
1.97 mmol) and 20% palladium hydroxide/carbon (0.10 g) in  
methanol (20 ml) was stirred at room temperature in a  
hydrogen atmosphere for 1.5 hours. The reaction mixture  
was filtered and the filtrate was concentrated under  
20 reduced pressure; the thus obtained residue was subjected  
to silica gel column chromatography (developing solvent:  
chloroform:methanol:aqueous ammonia = 100:10:1) to give  
N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.71 g, 99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers) δ 0.35,0.71,0.92 and  
25 0.96(6H,d,J=6.9Hz), 1.36 and 1.37(9H,s), 1.73-1.81 and  
2.03-2.17(1H,m), 1.74 and 2.23(3H,s), 2.64(1H,d,J=9.2Hz),  
2.90-3.04(1H,m), 2.93 and 3.00(3H,s), 3.19 and  
4.60(1H,dd,J=14.7,5.8 and 10.7,3.8Hz), 5.29,5.32 and

6.06(2H,brs), 5.59(1H,dd,J=10.4,5.8Hz), 6.54 and  
6.60(1H,d,J=7.9Hz), 6.79 and 6.93(1H,dd,J=7.9,2.0 and  
1.7Hz), 7.01 and 7.07(1H,d,J=2.0 and 1.7Hz), 8.10(1H,brs)

(8) Synthesis of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

5 To a solution of Z-Phe(4-F)-OH (1.09 g, 3.44 mmol),  
N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (1.04 g, 2.87 mmol) and CMPI  
(878 mg, 3.44 mmol) in THF (30 ml), TEA (0.96 ml, 6.88  
mmol) was added under cooling with ice and stirred at room  
temperature overnight. The reaction mixture was mixed with  
10 water and extracted with ethyl acetate. The organic layer  
was washed with saturated brine, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
under reduced pressure; the thus obtained residue was  
subjected to silica gel column chromatography (developing  
15 solvent: n-hexane:ethyl acetate =1:3) to give Z-Phe(4-F)-N-  
Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (1.73 g, 91%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers) δ 0.57,0.73,0.75 and  
0.90(6H,d,J=6.3-6.6Hz), 1.33 and 1.39(9H,s), 2.18-  
3.43(5H,m), 2.40 and 3.03(3H,s), 2.74 and 3.01(3H,s),  
20 4.62-5.49(7H,m), 5.95(1H,brs), 6.44(1H,d,J=7.9Hz), 6.57-  
7.35(12H,m)

(9) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

A mixture of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>  
(1.73 g, 2.61 mmol) and 10% palladium/carbon (340 mg) in  
25 methanol (50 ml) was stirred at room temperature in a  
hydrogen atmosphere for 17 hours. The reaction mixture was  
filtered and the filtrate was concentrated under reduced  
pressure; the thus obtained residue was subjected to silica

gel column chromatography (developing solvent:  
chloroform:methanol:aqueous ammonia = 100:10:1) to give  
Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (1.25 g, 91%).

EI-MS:528(M<sup>+</sup>)

- 5    <sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers) δ 0.50,0.76,0.79 and  
0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.39(9H,s), 2.19-  
2.95(5H,m), 2.50 and 3.03(3H,s), 2.81 and 3.02(3H,s), 3.17  
and 3.34(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.66 and  
3.84(1H,dd,J=8.9,4.6 and 8.6,4.6Hz), 4.91 and  
10 5.07(1H,d,J=10.6Hz), 5.07,5.19,5.30,5.98 and 6.64(2H,brs),  
5.49(1H,dd,J=10.6,5.9Hz), 6.35 and 6.62(1H,d,J=7.9Hz),  
6.74(2/3H,dd,J=7.9,1.7Hz), 6.95-7.11(19/3H,m)

#### Example 2

- 15    Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>  
(1) Synthesis of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

- To a solution of Boc-Phe(4-Cl)-OH (354 mg, 1.18 mmol),  
N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.33 g, 0.908 mmol) and CMPI  
(301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol)  
20 was added under cooling with ice and stirred at room  
temperature overnight. The reaction mixture was mixed with  
water and extracted with ethyl acetate. The organic layer  
was washed with saturated brine, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
25 under reduced pressure; the thus obtained residue was  
subjected to silica gel column chromatography (developing  
solvent: chloroform:methanol:aqueous ammonia = 40:1:0.05)  
to give Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.45 g,



77%).

(2) Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.45 g, 0.697 mmol) in methylene chloride (4 ml),  
5 TFA (3 ml) was added, stirred for 20 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with a saturated aqueous NaHCO<sub>3</sub> solution, and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and  
10 evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 30:1:0.1) to give Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (355 mg, 93%).

15 EI-MS: 544 and 546(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.49, 0.75, 0.78 and 0.93(6H, d, J=6.3-6.9Hz), 1.34 and 1.38(9H, s), 2.10-2.92(5H, m), 2.50 and 3.04(3H, s), 2.80 and 3.01(3H, s), 3.13 and 3.33(1H, dd, J=15.2, 5.9 and 13.9, 6.9Hz), 3.67 and  
20 3.85(1H, dd, J=8.9, 5.0 and 8.6, 5.0Hz), 4.90 and 5.06(1H, d, J=10.6Hz), 5.33, 5.41, 5.99 and 6.61(2H, brs), 5.49(1H, dd, J=10.6, 5.9Hz), 6.37 and 6.63(1H, d, J=7.9Hz), 6.72 and 6.98(1H, dd, J=7.9, 1.7Hz), 7.07-7.10(3H, m), 7.25-7.31(2H, m)

25

Example 3

Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Fmoc-Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-

NH<sub>2</sub>

To a solution of Fmoc-Phe(3,4-F<sub>2</sub>)-OH (500 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05), giving Fmoc-Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.56 g, 80%).

(2) Synthesis of Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Fmoc-Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.55 g, 0.715 mmol) in methylene chloride (5 ml), diethylamine (5 ml) was added, stirred for 4 hours and then evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:ethanol:aqueous ammonia = 60:1:0.1) to give Phe(3,4-F<sub>2</sub>)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (381 mg, 97%).

EI-MS: 546(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.51, 0.74, 0.79 and 0.93(6H, d, J=6.3-6.9 Hz), 1.33 and 1.38(9H, s), 2.10-2.93(5H, m), 2.51 and 3.03(3H, s), 2.83 and 3.01(3H, s), 3.17 and 3.33(1H, dd, J=14.8, 5.9 and 13.9, 6.6 Hz), 3.66 and

3.84(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and  
5.07(1H,d,J=10.6Hz), 5.41, 5.9(1H,brs), 5.41-5.51(1H,m),  
6.43 and 6.64(1H,d,J=7.9Hz), 6.75(2/5H,dd,J=7.9,1.7Hz),  
6.84-7.16(28/5H,m)

5

#### Example 4

Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Phe(3-F)-OH (0.20 g, 0.706 mmol),  
10 N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.21 g, 0.578 mmol) and CMPI  
(0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15  
mmol) was added under cooling with ice and stirred at room  
temperature overnight. The reaction mixture was mixed with  
water and extracted with ethyl acetate. The organic layer  
15 was washed with saturated brine, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
under reduced pressure; the thus obtained residue was  
subjected to silica gel column chromatography (developing  
solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05)  
20 to give Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.33 g,  
91%).

(2) Synthesis of Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-  
tBu)-NH<sub>2</sub> (0.33 g, 0.525 mmol) in methylene chloride (3 ml),  
25 TFA (1.5 ml) was added, stirred for 15 min. and then  
evaporated to remove the solvent under reduced pressure.  
The residue was mixed with methylene chloride, washed with  
a saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous

magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to  
 5 give Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (241 mg, 87%).

EI-MS:528(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers) δ 0.51,0.73,0.78 and 0.93(6H,d,J=6.3-6.6Hz), 1.33 and 1.38(9H,s), 2.10-2.96(5H,m), 2.46 and 3.03(3H,s), 2.78 and 3.01(3H,s), 3.16  
 10 and 3.35(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.70 and 3.90(1H,dd,J=8.3,5.6 and 8.6,5.0Hz), 4.89 and 5.06(1H,d,J=10.6Hz), 5.42, 5.99(1H,brs), 5.43-5.52(1H,m), 6.41 and 6.64(1H,d,J=7.9Hz), 6.72(2/5H,dd,J=7.9,1.7Hz), 6.83-6.99(18/5H,m), 7.10(2/5H,d,J=1.7Hz), 7.22-7.33(1H,m)

15

#### Example 5

Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Phe(2-F)-OH (0.20 g, 0.706 mmol),  
 20 N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer  
 25 was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing

solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05)  
to give Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.33 g,  
91%).

(2) Synthesis of Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

5 To a solution of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-  
tBu)-NH<sub>2</sub> (0.33 g, 0.525 mmol) in methylene chloride (3 ml),  
TFA (1.5 ml) was added, stirred for 15 min. and then  
evaporated to remove the solvent under reduced pressure.  
The residue was mixed with methylene chloride, washed with  
10 a saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
under reduced pressure. The thus obtained residue was  
subjected to silica gel column chromatography (developing  
solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to  
15 give Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (235 mg, 85%).

EI-MS: 528(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.45, 0.71, 0.79 and  
0.93(6H, d, J=5.9-6.6Hz), 1.31 and 1.38(9H, s), 2.10-  
2.89(5H, m), 2.47 and 3.06(3H, s), 2.76 and 3.01(3H, s), 3.14  
20 and 3.34(1H, dd, J=14.3, 5.9 and 13.9, 6.6Hz), 3.79 and  
3.95(1H, dd, J=8.4, 5.0 and 8.6, 4.3Hz), 4.88 and  
5.06(1H, d, J=10.6Hz), 5.37, 5.99(1H, brs), 5.41-5.51(1H, m),  
6.43(3/5H, d, J=7.9Hz), 6.56(2/5H, brs), 6.60-6.71(1H, m),  
6.92-7.29(6H, m)

25

Example 6

TFA salt of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>SO<sub>2</sub>Me

(1) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH<sub>2</sub>SO<sub>2</sub>Me

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To a solution of crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-  
OH (0.95 g, 2.0 mmol), WSCI·HCl (0.77 g, 3.99 mmol) and  
methanesulfonamide (0.29 g, 3.0 mmol) in DMF (15 ml), DMAP  
(0.49 g, 0.99 mmol) was added under cooling with ice and  
5 stirred at room temperature overnight. The mixture was  
mixed with water and then with 2N hydrochloric acid,  
extracted with ethyl acetate. The organic layer was washed  
with saturated brine, dried over anhydrous magnesium  
sulfate and evaporated to remove the solvent under reduced  
10 pressure. The thus obtained residue was subjected to  
silica gel column chromatography (developing solvent: ethyl  
acetate:n-hexane = 2:1) to give the titled compound (0.83 g,  
75%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36(9H,s), 2.80(s,3H), 2.97-3.30(m,2H),  
15 3.21(s,3H), 4.60-4.74(m,1H), 5.08(s,2H), 5.13(s,2H),  
6.81(d,1H,J=8.2Hz), 6.86-7.13(m,2H), 7.20-7.46(m,10H),  
9.0(brs,1H)

#### (2) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-NH<sub>2</sub>SO<sub>2</sub>Me

A mixture of Z-N-Me-Tyr(3-tBu-4-benzyloxy)-NH<sub>2</sub>SO<sub>2</sub>Me  
20 (0.80 g, 1.45 mmol) and 20% palladium hydroxide/carbon  
(0.09 g) in methanol (15 ml) was stirred at room  
temperature overnight in a hydrogen atmosphere. The  
reaction mixture was filtered and the filtrate was  
evaporated to remove the solvent under reduced pressure,  
25 giving crude N-Me-Tyr(3-t-Bu)-NH<sub>2</sub>SO<sub>2</sub>Me (0.53 g).

To a solution of the crude N-Me-Tyr(3-t-Bu)-NH<sub>2</sub>SO<sub>2</sub>Me  
(0.51 g, 1.43 mmol), Z-N-Me-Val-OH 0.49 g, 1.86 mmol) and  
CMPI (0.51 g, 2.00 mmol) in THF (10 ml), TEA (0.60 ml, 4.29

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mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water, rendered acidic by the addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic layer  
5 was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 0.5% acetic acid) to give  
10 the titled compound (0.70 g, in 2 steps, 85%).

(3) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO<sub>2</sub>Me

A mixture of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO<sub>2</sub>Me (0.65 g, 1.13 mmol) and 20% palladium hydroxide/carbon  
15 (0.09 g) in methanol (10 ml) was stirred at room temperature for 2.5 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO<sub>2</sub>Me (0.50 g).

20 To a solution of the above crude compound (0.48 g, 1.09 mmol), Boc-Phe(4-F)-OH 0.40 g, 1.41 mmol) and CMPI (0.39 g, 1.53 mmol) in THF (8 ml), TEA (0.46 ml, 3.27 mmol) was added under cooling with ice and stirred at room temperature overnight for 22 hours. The reaction mixture  
25 was mixed with water, rendered acidic by the addition of 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue  
was subjected to silica gel column chromatography  
(developing solvent: ethyl acetate:n-hexane = 2:3  
containing 5% acetic acid) to give the titled compound  
5 (0.50 g, in 2 steps, 65%).

(4) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-NH<sub>2</sub>Me  
TFA salt

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-  
Bu)-NH<sub>2</sub>Me (208 mg, 0.294 mmol) in methylene chloride (6  
10 ml), TFA (3 ml) was added and stirred for 1.5 hours. The  
reaction mixture was evaporated under reduced pressure; the  
thus obtained residue was dissolved in a mixture of  
acetonitrile/water (1:10) (80 ml), which mixture containing  
0.1% TFA, and lyophilized to give the titled compound (0.20  
15 g, 94%).

EI-MS: 606(M<sup>+</sup>)

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): (three rotamers) δ 0.02(d, 3/5H, J=5.9Hz),  
0.22(d, 3/5H, J=5.9Hz), 0.62(d, 3/5H, J=7.6Hz),  
0.68(d, 3/5H, J=6.6Hz), 0.77(d, 9/5H, J=6.6Hz),  
20 0.89(d, 9/5H, J=6.3Hz), 1.28(s, 27/5H), 1.31(s, 9/5H),  
1.35(s, 9/6H), 1.86-2.03(m, 2/7H), 2.15-2.28(m, 5/7H), 2.5-  
3.4(m, 10H), 4.35-4.62(m, 1H), 4.80-5.02(1H), 5.11-5.42(m, 1H),  
6.55-7.18(m, 7H), 8.0-8.2(m, 3H), 8.98-9.06(m, 1H),  
11.2(brs, 1H)

25

Example 7

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

(1) Synthesis of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe





6.95(1H,dd,J=2.8,3.4Hz), 7.13(1H,d,J=3.15Hz)

(3) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of N-Me-Tyr(3-tBu)-NHOMe (1.24 g, 4.42 mmol), Z-N-Me-Val-OH (1.76 g, 6.63 mmol) and CMPI (1.7 g, 6.63 mmol) in THF (30 ml), TEA (1.23 ml, 8.84 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1) to give the titled compound (1.32 g, 57%).

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta$  0.43(3H,m), 0.80(3H,m), 1.36(9H,s), 3.02(9H,m), 3.65(3H,s), 4.4(1H,m), 5.1(3H,m), 6.4-7.4(8H,m)

(4) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (1.23 g, 2.33 mmol) in MeOH (20 ml), palladium hydroxide/carbon (350 mg) was added and stirred in a hydrogen atmosphere for 1 hour. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure to give crude N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (0.91 g).

A solution of the thus obtained crude compound (0.98 g, 2.5 mmol), Boc-Phe(4-F)-OH (0.92 g, 3.25 mmol) and CMPI (0.83 g, 3.25 mmol) in THF 20 ml, TEA (0.52 ml, 3.75 mmol) was added and stirred overnight. The mixture was mixed with water, extracted with ethyl acetate. The organic

layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (972 mg, 56%).

(6) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (972 mg, 1.508 mmol) in methylene chloride (10 ml), TFA (7 ml) was added and stirred for 30 min. The mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (288 mg, 34%).

15 EI-MS: 558 (M<sup>+</sup>)

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 0.42 (3H, d, J=13.5 Hz), 0.79 (3H, d, J=13.2 Hz), 1.33 (9H, s), 2.10 (1H, m), 2.60 (1H, m), 2.90 (2H, m), 2.91 (3H, s), 3.07 (3H, s), 3.28 (1H, m), 3.68 (3H, s), 3.91 (1H, m), 4.82 (1H, d, J=10.7 Hz), 5.13 (1H, m), 6.60 (1H, d, J=10.4 Hz), 6.89 (1H, m), 7.0-7.3 (5H, m), 9.1 (1H, m)

Example 8

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of Z-Tyr(3-tBu)-OH (3.04 g, 8.19 mmol)

in THF (8.2 ml), under cooling with ice N,N-carboxyldiimidazole (1.59 g, 9.83 mmol) was added and stirred for 1 hour. To the mixture, 2-aminopyridine (925 mg, 9.83 mmol) was then added and stirred for 2 hours under  
5 cooling with ice and then further 6.5 hours at room temperature. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure.

10 The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.16 g, 59%).

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta$  1.24(9H,s), 2.95-3.20(2H,m), 4.45-4.60(1H,m), 5.11(2H,dd,J=17.5,12.2Hz), 6.53(1H,d,J=7.9Hz),  
15 6.85(1H,d,J=7.9Hz), 6.95-7.15(2H,m), 7.32(5H,brs), 7.67-7.73(1H,m), 8.15-8.25(2H,m)

(2) Synthesis of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (2.16 g, 4.83 mmol) in  
20 methanol (160 ml), 10% palladium/carbon (400 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced  
25 pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 10:1:100), giving the titled compound (1.48 g, 98%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36(9H,s), 2.72-3.23(2H,m), 3.67-  
3.72(1H,m), 6.62(1H,d,J=7.9Hz), 6.85-6.88(1H,m), 6.95-  
7.20(2H,m), 7.70-7.77(1H,m), 8.29-8.39(2H,m)

(3) Synthesis of 2-(N-benzyloxycarbonyl-N-methylamino)-3-  
5 methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-  
pyridylcarbamoyl)ethylamide

To a solution of 3-tert-butyl-4-hydroxyphenylalanyl  
(2-pyridyl)amide (1.48 g, 4.73 mmol), Z-N-Me-Val-OH (1.63 g,  
6.15 mmol) and CMPI (1.57 g, 6.15 mmol) in THF 30 ml, TEA  
10 (1.5 ml, 10.88 mmol) was added under cooling with ice and  
stirred for 3 hours under cooling with ice. The mixture  
was mixed with water and extracted with ethyl acetate. The  
organic layer was washed with saturated brine, dried over  
anhydrous magnesium sulfate and evaporated to remove the  
15 solvent under reduced pressure; the thus obtained residue  
was subjected to silica gel column chromatography  
(developing solvent: ethyl acetate:n-hexane = 1:2), giving  
the titled compound (1.74 g, 65%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.70-0.95(6H,m), 1.26(9H,s), 2.20-  
20 2.35(1H,m), 2.70-3.10(5H,m), 4.00-4.20(1H,m), 4.65-  
4.80(1H,m), 5.17(2H,brs), 6.44(1H,d,J=7.6Hz), 6.60-6.85(1H,  
m), 6.95-7.10(2H,m), 7.36(5H,brs), 7.60-7.75(1H,m), 8.10-  
8.25(2H,m)

(4) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-  
25 tert-butyl-4-hydroxyphenyl)-1-(2-  
pyridylcarbamoyl)ethylamide

To a solution of 2-(N-benzyloxycarbonyl-N-  
methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-

hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.74 g, 3.10 mmol) in methanol (50 ml), 10% palladium carbon (300 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 5:0.1:100), giving the titled compound (1.30 g, 98%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.69(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.31(9H,s), 1.95-2.11(1H,m), 2.36(3H,s), 2.81(1H,d,J=4.6Hz), 2.99-3.18(2H,m), 4.73-4.81(1H,m), 6.59(1H,d,J=7.9Hz), 6.94(1H,dd,J=7.9,2.0Hz), 7.00-7.10(2H,m), 7.65-7.72(1H,m), 7.80(1H,d,J=7.9Hz), 8.18(1H,d,J=8.6Hz), 8.25(1H,d,J=4.6Hz),

(5) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.25 g, 2.93 mmol), Boc-Phe(4-F)-OH (1.08 g, 3.81 mmol) and CMPI (973 mg, 3.81 mmol) in THF 19 ml, TEA (0.94 ml, 6.74 mmol) was added under cooling with ice and stirred for 4 hours under cooling with ice. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure;

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the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.72 g, 85%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.65-1.02(6H,m), 1.26(9H,s), 1.34(9H,s),  
5 2.20-2.40(1H,m), 2.75-3.15(4H,m), 2.89(3H,s), 4.20-  
4.35(1H,m), 4.70-5.00(2H,m), 6.61(1H,d,J=7.9Hz), 6.75-  
7.20(7H,m), 7.60-7.80(1H,m), 8.20-8.30(2H,m)  
(6) 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide  
10

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.67 g, 2.41 mmol) in  
15 methylene chloride (30 ml), TFA (5 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated under reduced pressure; the thus obtained residue was mixed with chloroform, washed with a saturated aqueous NaHCO<sub>3</sub> solution and saturated brine,  
20 dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled  
25 compound (370 mg).

EI-MS: 591(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.74(2H,d,J=6.9Hz), 0.77(1H,d,J=6.9Hz),  
0.88(1H,d,J=6.3Hz), 0.95(2H,d,J=6.3Hz), 1.25(9H,s), 2.24-

2.44(1H,m), 2.50-3.25(4H,m), 2.78(2.4H,s), 2.85(0.6H,s),  
3.55-3.65(0.8H,m), 3.80-3.90(0.2H,m), 4.00(0.8H,d,J=10.9Hz),  
4.36(0.2H,d,J=10.9Hz), 4.65-4.80(0.2H,m), 4.90-5.00(0.8H,m),  
6.55-7.20(8H,m), 7.65-7.75(1H,m), 8.15-8.25(2H,m)

5

#### Example 9

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

#### 10 (1) Synthesis of Z-3-tBu-tyrosinol

To a solution of Z-Tyr(3-tBu)-OMe (7.4 g, 19 mmol) in THF (190 ml), lithium borohydride (1.25 g, 57.4 mmol) was added under cooling with ice and stirred for 1.5 hours at room temperature. The mixture was mixed with a saturated aqueous NH<sub>4</sub>Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (6.8 g, 99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.38(9H,s), 2.15(1H,m),  
2.78(2H,brd,J=6.9Hz), 3.5-3.8(2H,m), 3.8-4.0(1H,m),  
4.86(1H,s), 4.9-5.0(1H,m), 5.09(2H,s), 6.58(1H,d,J=7.9Hz),  
6.88(1H,brd,J=7.9Hz), 7.05(1H,brs), 7.34(5H,s)

#### 25 (2) Synthesis of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of Z-3-tBu-tyrosinol (2 g, 5.6 mmol),



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triphenylphosphine (1.76 g, 6.7 mmol), phthalimide (0.99 g, 6.7 mmol) in THF 50 ml, diethyl azodicarboxylate (DEAD) (1.05 ml, 6.7 mmol) was added under cooling with ice and stirred at the same temperature for 1 hour. The mixture  
5 was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography  
10 (developing solvent: hexane:ethyl acetate = 2:1) to give (1-(1,3-dihydro-1,3-dioxo-isoindol-2-yl)methyl-2-(3-tBu-4-hydroxyphenyl)ethyl)carbamic acid benzyl ester (3.2 g).

To the above compound (3.2 g), a 40% methylamine methanol solution (40 ml) was added at room temperature and  
15 stirred at the same temperature for 10 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the  
20 titled compound (1.9 g).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.37(9H,s), 2.6-2.9(4H,m), 3.7-3.9(4/5H,m), 3.9-4.1(1/5H,m) 4.8-4.9(4/5H,m), 5.09(2H,s), 5.4-5.5(1/5H,m), 6.5-6.6(1H,m), 6.84(1H,d,J=7.3Hz), 6.9-7.1(1H,m), 7.33(5H,s)

25 (3) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

A mixture of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (1.0 g, 2.8 mmol), potassium

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cyanate (0.5 g, 5.5 mmol), acetic acid (0.5 ml), dioxane (10 ml) and water (10 ml) was stirred at 60°C for 2 hours. The mixture was mixed with a saturated aqueous NaHCO<sub>3</sub> solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:methanol = 50:1), giving the titled compound (0.9 g, 80%).

<sup>1</sup>H-NMR(CD<sub>3</sub>OD): δ 1.35(9H,s), 2.5-2.8(2H,m), 3.0-3.2(1H,m), 3.2-3.4(1H,m), 3.7-3.9(1H,m), 5.01(2H,d,J=3.6Hz), 6.63(1H,d,7.9Hz), 6.84(1H,brd,J=7.9Hz), 7.04(1H,brs), 7.2-7.4(5H,m)

(4) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.9 g, 2.26 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.54 g).

To a solution of the above compound (0.53 g, 2 mmol), Z-N-Me-Val-OH (0.69 g, 2.6 mmol) and CMPI (0.67 g, 2.6 mmol) in THF (20 ml), TEA (1 ml, 7.2 mmol) was added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and

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extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

5 column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.98 g, 98%).

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta$  0.82(3H,d,J=6.3Hz), 0.88(3H,d,J=6.3Hz), 1.35(9H,s), 2.1-2.3(1H,m), 2.6-2.8(2H,m), 2.76(3H,s),  
10 3.0-3.4(2H,m), 3.9-4.1(1H,m), 4.7-5.0(2H,m), 5.0-5.1(2H,m), 5.5-5.6(1H,m), 6.4-7.0(5H,m), 7.34(5H,s)

(5) Synthesis of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

15 To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.97 g, 1.95 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3  
20 hours. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure, giving N-(2-(2-amino-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.72 g).

To a solution of the above crude compound (0.64 g, 1.85 mmol), Boc-Phe(4-F)-OH (0.63 g, 2.22 mmol) and CMPI (0.57 g, 2.23 mmol) in THF (18 ml), TEA (0.93 ml, 6.67 mmol) was added under cooling with ice and stirred at room temperature for 8 hours. The mixture was mixed with water

and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

- 5 column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.79 g, 66%).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): δ 0.70, 0.75, 0.85, and 0.95(total 6H,d,J=5.9-6.3Hz), 1.2-1.4(18H,m), 2.0-2.1(1H, m),  
 10 2.4-2.9(7H,m), 2.9-3.1(2H,m), 3.8-4.0(1H,m), 4.3-4.6(2H,m), 5.39, 5.51(2H,brs), 5.74(1H,d,J=1.3Hz), 5.9-6.0(1H,m), 6.6-6.9(2H,m), 6.9-7.1(2H,m), 7.1-7.3(3H,m), 7.60 and 7.73(total 1H, brd), 9.02(1H,s)

- (6) Synthesis of N-(2-(2-((2-amino-3-(4-  
 15 fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea  
 20 (0.75 g) in methylene chloride (6 ml), TFA (6 ml) was added under cooling with ice, stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous NaHCO<sub>3</sub>  
 25 solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent:

chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (480 mg, 76%).

FAB-MS: 544 ( $M^+ + 1$ )

$^1\text{H-NMR}$ (DMSO- $d_6$ ):  $\delta$  0.49, 0.73, and 0.85 (total 6H, d,  $J=6.0$ -  
5 6.6 Hz), 1.30 and 1.32 (total 9H, s), 2.0-2.2 (1H, m), 2.4-  
3.1 (9H, m), 3.7-4.1 (3H, m), 4.52 and 5.48 (total 2H, m),  
5.8-6.0 (1H, m), 6.6-6.8 (2H, m), 6.9-7.3 (5H, m), 7.67 and  
8.79 (total 1H, d,  $J=7.6$ -8.6 Hz), 9.01 and 9.06 (total 1H, s)

10 Example 10

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

(1) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester  
15

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)amine (1.46 g, 4.1 mmol) in dioxane (8 ml), an aqueous sodium carbonate solution (0.44 g, 4.1 mmol) (8 ml) and  $(\text{Boc})_2\text{O}$  (0.9 g, 4.1 mmol) were  
20 added in that order under cooling with ice and stirred at the same temperature for 2.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under  
25 reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.7 g, 91%).

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<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.38(9H,s), 1.42(9H,s), 2.6-2.9(2H,m),  
3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.7-4.8(1H,m), 5.08(2H,s),  
6.58(1H,d,J=8.9Hz), 6.85(1H,brd,J=8.9Hz), 7.03(1H,brs),  
7.2-7.5(5H,m)

- 5 (2) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.6 g,  
10 3.5 mmol) in methanol (35 ml), 10% palladium carbon (160 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1.5 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-((2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu  
15 ester (1.1 g).

To a solution of the thus obtained crude compound (1.1 g, 3.42 mmol), Z-N-Me-Val-OH (1.08 g, 4.08 mmol) and CMPI (1.04 g, 4.07 mmol) in THF (35 ml), TEA (1.7 ml, 12.2 mmol) was added under cooling with ice and stirred at room  
20 temperature for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica  
25 gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.8 g, 93%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.82(3H,d,J=6.6Hz), 0.90(3H,d,J=6.2Hz),  
1.37(9H,s), 1.42(9H,s), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.0-

3.3(2H,m), 3.9-4.3(2H,m), 5.13(2H,s), 6.44(1H,d,J=7.9Hz),  
6.75(1H,brd,J=7.9Hz), 7.00(1H,brs), 7.36(5H,s)

(3) Synthesis of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-

5 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.8 g, 3.16  
10 mmol) in methanol (35 ml), 10% palladium carbon (180 mg) was added and stirred for 1 hour in a hydrogen atmosphere at room temperature. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-(2-(N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.33 g).  
15

To a solution of the thus obtained crude compound (1.33 g, 3.15 mmol), Z-Phe(4-F)-OH (1.2 g, 3.78 mmol) and CMPI (0.97 g, 3.78 mmol) in THF (35 ml), TEA (1.6 ml, 11.5 mmol) was added under cooling with ice and stirred at room  
20 temperature for 10 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica  
25 gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.48 g, 53%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.68, 0.75, 0.91, and 0.98(total 6H,d,J=6.2-6.9Hz), 1.35,1.37,1.40, and 1.42(total 18H,m),

2.1-3.4(10H,m), 4.0-4.5, 4.7-5.1, and 5.5-5.7(total 7H,m),  
6.3-7.5(17H, m)

(4) Synthesis of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-

5 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.38 g) in  
10 methylene chloride (5 ml), TFA (5 ml) was added under cooling with ice, stirred at room temperature for 30 min. and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous NaHCO<sub>3</sub> solution, dried over  
15 anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (1.1 g, 92%).

20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.67,0.76,0.92,and 0.97(total 6H,d,J=6.6-6.9Hz), 1.35 and 1.37(total 9H,s), 2.2-2.5(1H,m), 2.4-3.1(9H,m), 4.0-4.2 and 4.4-4.5(total 2H,m), 4.7-5.1(2H,m), 5.5-5.6 and 5.7-5.9(total 1H,brd,J=7.6-8.1Hz), 6.2-6.4, 6.5-6.7, and 6.8-7.4(total 13H,m)

25 (5) Synthesis of N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine



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To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (580 mg, 0.91 mmol) in DMF (4.5 ml), 1H-pyrazole-1-carboxamide hydrochloride (161 mg, 1.09 mmol) and DIEA (0.19 ml, 1.09 mmol) were added at room temperature and stirred at the same temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 100:1 to 10:1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine (410 mg).

To a solution of the above compound (410 mg) in methanol (20 ml), 10% palladium carbon (40 mg) was added and stirred in a hydrogen atmosphere at room temperature for 5 hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 5:1), giving the titled compound (250 mg, 76%).

FAB-MS: 543( $M^+ + 1$ )

$^1\text{H-NMR}(\text{CD}_3\text{OD})$ :  $\delta$  0.47, 0.53, 0.80, 0.90(6H,d,J=6.3-6.9Hz), 1.31, 1.37(9H,s), 2.0-2.3(1H,m), 2.41, 2.46, and 2.57(total

3H,s), 2.5-3.4(6H,m), 3.8-4.6(3H,m), 6.6-7.3(7H,m)

#### Example 11

Synthesis of N-(2-(2-((2-amino-3-(4-  
5 fluorophenyl)propionyl)-N-methylamino)-3-  
methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-  
cyano-N''-methylguanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-  
(4-fluorophenyl)propionyl)-N-methylamino)-3-  
10 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine  
(500 mg, 0.79 mmol) in ethanol (4 ml), dimethyl N-  
cyanodithioiminocarbonate (127 mg, 0.87 mmol) was added at  
room temperature and stirred at the same temperature for 16  
hours. The reaction mixture was concentrated under reduced  
15 pressure; the thus obtained residue was mixed with a 40%  
methylamine methanol solution (5 ml) at room temperature  
and stirred at the same temperature for 16 hours. The  
reaction mixture was concentrated under reduced pressure  
and the thus obtained residue was subjected to silica gel  
20 column chromatography (developing solvent:  
chloroform:methanol:aqueous ammonia = 20:1:0.1) to give N-  
(2-(2-((2-(benzyloxycarbonylamino)-3-(4-  
fluorophenyl)propionyl)-N-methylamino)-3-  
methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-  
25 cyano-N''-methylguanidine (450 mg).

To a solution of the above compound (440 mg) in  
methanol (6 ml), 10% palladium carbon (50 mg) was added and  
stirred in a hydrogen atmosphere at room temperature for 15

hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (280 mg, 78%).

FAB-MS:582(M<sup>+</sup>+1)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.62, 0.79, 0.87, and 0.91(total 6H,d,J=6.3-6.6Hz), 1.37 and 1.40(total 9H,s), 2.1-2.4(1H,m), 2.5-3.0(10H,m), 3.1-3.4(2H,m), 3.6-4.4(3H,m), 5.8-6.1(1H,m), 6.6-7.2(7H,m), 8.68(1H,d,J=6.6Hz)

#### Example 12

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (514 mg, 0.811 mmol) in 1,4-dioxane (8 ml), sulfamide (156 mg, 1.62 mmol) was added and stirred at 120°C for 5 hours. The reaction mixture was evaporated under reduced pressure to remove the solvent; the thus obtained residue was mixed with water, and extracted with chloroform. The organic layer was washed

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with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (397 mg, 69%).

$^1\text{H-NMR}(\text{CDCl}_3)$ : (two rotamers)  $\delta$  0.69, 0.85 and 0.99(6H, d,  $J=6.3-6.6\text{Hz}$ ), 1.36 and 1.37(9H, s), 1.80-1.90(1H, m), 2.22-2.40(1H, m), 2.43 and 2.81(3H, s), 2.60-3.10(4H, m), 3.26-3.38(1H, m), 3.70-3.80(1H, m), 3.90-4.10(1H, m), 4.28-4.44(1H, m), 4.72-5.30(3H, m), 5.03(2H, s), 6.52-6.66(2H, m), 6.80-7.40(10H, m)

(2) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

A mixture of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide (332 mg, 0.466 mmol) and 10% palladium carbon (40 mg) in methanol (5 ml) was stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 200:10:1), giving the titled compound (180 mg, 67%).

FAB-MS: 580( $\text{M}+\text{H}^+$ )

$^1\text{H-NMR}(\text{CDCl}_3)$ : (two rotamers)  $\delta$  0.63, 0.75, 0.81 and

0.93(6H,d,J=6.3-6.6Hz), 1.38 and 1.39(9H,s), 2.20-3.42(6H,m), 2.60 and 3.02(3H,s), 3.49(1H,s), 3.60-3.90(2H,m), 4.30-4.44(1H,m), 5.30-5.40(1H,m), 6.56-7.16(7H,m), 8.34-8.42(1H,m)

5

#### Example 13

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

- 10 (1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester

- To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (1.17 g, 1.84 mmol) in ethanol (18 ml), ethyl glyoxylate (0.7 ml, 2.76 mmol), acetic acid (1.8 ml) and sodium cyanoborohydride (173 mg, 2.76 mmol) were added and stirred for 1 hour. The reaction mixture was mixed with a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate:methylene chloride = 2:3:1), giving the titled compound (900 mg, 68%).
- 15
- 20
- 25

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.65,0.75,0.91 and  
0.97(6H,d,J=6.2-6.9Hz), 1.22 and 1.29(3H,t,J=7.2Hz), 1.35  
and 1.36(9H,s), 2.22-2.40(1H,m), 2.42 and 2.90(3H,s), 2.60-  
3.02(5H,m), 3.22-3.46(2H,m), 4.06-4.28(2H,m),  
5 4.47(1H,d,J=12.2Hz), 4.80-5.12(3H,m), 5.29(2H,s),  
5.74(1H,d,J=8.9Hz), 6.58-7.42(12H,m)

(2) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-  
fluorophenylpropanoyl-N-methylamino)-3-  
methyl)butyrylamino)-3-(3-tert-butyl-4-  
10 hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-  
fluorophenylpropanoyl-N-methylamino)-3-  
methyl)butyrylamino)-3-(3-tert-butyl-4-  
hydroxyphenyl)propylaminoacetic acid ethyl ester (889 mg,  
15 1.23 mmol) in methanol (24 ml), aqueous ammonia (16 ml)  
was added and stirred for 15 hours at room temperature.  
The reaction mixture was evaporated to remove the solvent  
under reduced pressure, extracted with ethyl acetate and  
washed with saturated brine. The resultant was dried over  
20 anhydrous magnesium sulfate and evaporated to remove the  
solvent under reduced pressure; the thus obtained residue  
was subjected to silica gel column chromatography  
(developing solvent: chloroform:methanol:aqueous ammonia =  
110:10:1), giving the titled compound (600 mg, 70%).

25 <sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.65,0.75,0.90 and  
0.96(6H,d,J=6.0-6.6Hz), 1.36 and 1.37(9H,s), 2.22-  
2.40(1H,m), 2.47 and 2.82(3H,s), 2.60-3.02(4H,m), 3.24 and  
3.26(2H,s), 4.02-4.38(2H,m), 4.76-5.08(3H,m), 5.40-

5.90(3H,m), 6.56-7.38(12H,m)

(3) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

- 5 To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide (595 mg, 0.860 mmol) in methanol (10 ml), 20% palladium hydroxide/carbon (150 mg) was added and stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol:hexane = 10:1:1), giving the titled compound (333 mg, 70%).

FAB-MS:558(M+H<sup>+</sup>)

- <sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.66,0.79 and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.39(9H,s), 2.22-2.38(1H,m), 2.63 and 2.91(3H,s), 2.50-2.82(4H,m), 3.12-3.28(2H,m), 3.58-3.88(2H,m), 4.18-4.40(2H,m), 5.50-5.70(1H,m), 6.58-7.14(8H,m)

#### Example 14

- N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminoethyl)-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
- (1) Synthesis of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine





methylene chloride:methanol = 10:1), giving the titled compound (2.45 g, 49%).

(3) N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide

5 To a solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine (1.27 g, 2.84 mmol) in methylene chloride (29 ml), TEA (0.6 ml, 4.26 mmol) and then methanesulfonyl chloride (0.3 ml, 3.69 mmol) were added slowly under cooling with ice. After stirring for 30  
10 min., the mixture was mixed with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene  
15 chloride:ethyl acetate:n-hexane = 1:1:2), giving the titled compound (1.23 g, 83%).

(4) Synthesis of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

20 N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide (1.2 g, 2.29 mmol) was dissolved in a mixture of methanol (23 ml) and methylene chloride (5 ml), mixed with palladium hydroxide/carbon (0.60g) and stirred for 12 hours in a  
25 hydrogen atmosphere. After filtering off insoluble material using Celite, the filtrate was concentrated to give crude N-[2-amino-3-(4-benzyloxy-3-tert-butylphenyl)propyl]methanesulfonamide (0.68 g).



concentrated; to a solution of the thus obtained residue  
(0.75 g), Z-Phe(4-F)-OH (748 mg, 2.66 mmol) and CMPI (602  
mg, 2.36 mmol) in THF 18 ml, TEA (0.82 ml, 5.44 mmol) was  
added under cooling with ice. The mixture was stirred at  
5 room temperature overnight, mixed with a saturated aqueous  
sodium bicarbonate solution and extracted with ethyl  
acetate. The organic layer was dried over magnesium  
sulfate and evaporated to remove the solvent under reduced  
pressure; the thus obtained residue was subjected to silica  
10 gel column chromatography (developing solvent: methylene  
chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled  
compound (827 mg, 64%).

(6) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-  
(methanesulfonylaminomethyl)ethyl]-2-[N-(4-  
15 fluorophenylalaninoyl)methylamino]-3-methylbutanamide

To a solution of 2-[N-(N-benzyloxycarbonyl-4-  
fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-  
hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-  
methylbutanamide (680 mg, 0.95 mmol) in methanol (10 ml),  
20 palladium hydroxide/carbon (0.25 g) was added and stirred  
in a hydrogen atmosphere for 1 hour. After filtering off  
insoluble material using Celite, the filtrate was  
concentrated; the thus obtained residue was subjected to  
silica gel column chromatography (developing solvent:  
25 chloroform:methanol:concentrated aqueous ammonia =  
100:10:1), giving the titled compound (494 mg, 89%).

EI-MS: 578(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.62(d, 21/10H, J=6.9Hz),

0.75(d,9/10H,J=6.6Hz), 0.84(d,9/10H,J=6.6Hz),  
0.93(d,21/10H,J=6.3Hz), 1.36(s,27/10H), 1.39(s,63/10H),  
2.20-2.45(m,1H), 2.46-2.95(m,8H), 3.02-3.17(m,3H), 3.61-  
4.05(m,2H), 4.18-4.37(m,1H), 4.87-4.95(m,7/10H), 5.23-  
5 5.35(m,3/10H), 5.55-5.70(m,3/10H), 6.20-6.50(m,7/10H),  
6.60-7.20(m,7H), 8.01(d,1H,J=7.6Hz)

#### Example 15

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-  
10 methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-  
carbamidomethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-  
hydroxymethylethyl carbamic acid benzyl ester

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (2.46 g,  
15 5.19 mmol) in THF (50 ml), lithium borohydride (339 mg,  
15.57 mmol) was added under cooling with ice and stirred at  
room temperature for 3 hours. The reaction mixture was  
mixed with a saturated aqueous ammonium chloride solution  
and extracted with ethyl acetate. The organic layer was  
20 washed with saturated brine, dried over anhydrous magnesium  
sulfate and evaporated to remove the solvent under reduced  
pressure; the thus obtained residue was subjected to silica  
gel column chromatography (developing solvent: n-  
hexane:ethyl acetate = 2:1), giving the titled compound  
25 (2.30 g, 99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.38(9H,s), 2.11(1H,brs),  
2.80(2H,d,J=6.9Hz), 3.54-3.77(2H,m), 3.83-3.97(1H,m), 4.88-  
4.97(1H,m), 5.09(4H,s), 6.85(1H,d,J=8.3Hz),

6.97(1H,dd,J=8.3,1.8Hz), 7.11(1H,d,J=1.8Hz), 7.27-  
7.50(10H,m)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester

5 To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (1.87 g, 4.18 mmol) in pyridine (42 ml), methanesulfonyl chloride (0.36 ml, 4.60 mmol) was added under cooling with ice. After stirring for 1 hour, the mixture was mixed with water and  
10 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving the titled compound (1.93 g, 88%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.38(9H,s), 2.76-2.92(2H,m), 2.96(3H,s),  
15 4.10-4.21(2H,m), 4.21-4.32(1H,m), 4.88-5.00(1H,m), 5.09(4H,s), 6.86(1H,d,J=8.6Hz), 6.98(1H,brd,J=7.9Hz), 7.11(1H,brs), 7.30-7.48(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester

20 To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester 1.93 g, 4.23 mmol) in DMSO (11 ml), potassium cyanide (827 mg, 12.7 mmol) was added and heated at 70°C. After stirring for 4 hours, the mixture was mixed with water and extracted  
25 with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.42 g, 74%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.38(9H,s), 2.46(1H,dd,J=16.8,4.0Hz),  
2.74(1H,dd,J=16.8,4.6Hz), 2.82(1H,dd,J=13.8,8.4Hz),  
5 2.96(1H,dd,J=13.8,6.5Hz), 4.07-4.18(1H,m), 4.89-4.98(1H,m),  
5.09(4H,s), 6.87(1H,d,J=8.3Hz), 6.99(1H,dd,J=8.3,1.5Hz),  
7.12(1H,d,J=1.5Hz), 7.36-7.47(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine

10 To a solution of 2-(4-benzyloxy-3-tbutylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the  
15 reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

A mixture of the above crude compound, 20% palladium  
20 hydroxide/carbon (0.50 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography  
25 (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (639 mg, 84%).

$^1\text{H-NMR}(\text{DMSO}): \delta$  1.33(9H,s), 1.96(1H,dd,J=14.5,8.6Hz),  
2.12(1H,dd,J=14.5,4.0Hz), 2.37(1H,dd,J=13.4,7.4Hz),

2.46-2.55(1H,m), 3.07-3.20(1H,m), 6.68(1H,d,J=8.2Hz),  
6.73(1H,brs), 6.79(1H,brd,J=8.2Hz), 7.40(1H,brs),  
9.05(1H,s)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-  
5 methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-  
carbamidomethylethylamide

To a solution of Z-N-Me-Val-OH (736 mg, 2.78 mmol),  
2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine  
(579 mg, 2.32 mmol) and CMPI (710 mg, 2.78 mmol) in THF (23  
10 ml), TEA (0.77 ml) was added under cooling with ice and  
stirred at room temperature for 4 hours. The reaction  
mixture was mixed with water and extracted with ethyl  
acetate. The organic layer was washed with saturated brine,  
dried over anhydrous magnesium sulfate and evaporated to  
15 remove the solvent under reduced pressure; the thus  
obtained residue was subjected to silica gel column  
chromatography (developing solvent: ethyl acetate), giving  
the titled compound (1.09 g, 95%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.78-0.90(6H,m), 1.37(9H,s), 2.14-  
20 2.80(5H,m), 2.72(3H,s), 3.92-4.04(1H,m), 4.32-4.48(1H,m),  
5.04,5.15(2H,brs), 5.27-5.37(1H,m), 5.78,6.03(1H,brs),  
6.38-6.82(3H,m), 7.04(1H,brs), 7.30-7.41(5H,m).

(6) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-  
t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

25 To a solution of 2-(benzyloxycarbonyl)methylamino-3-  
methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-  
carbamidomethylethylamide (1.04 g, 2.09 mmol) in methanol  
(20 ml), 10% palladium carbon (100 mg) was added and

stirred in a hydrogen atmosphere at room temperature for 1 hour. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.67 g, 88%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.68(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.82-1.97(1H,m), 2.27(3H,s), 2.45(1H,dd,J=15.8,7.3Hz), 2.68(1H,d,J=4.6Hz), 2.78-2.91(2H,m), 4.41-4.56(1H,m), 5.30(1H,brs), 5.58(1H,brs), 6.34(1H,brs), 6.62(1H,d,J=8.0Hz), 6.92(1H,dd,J=8.0,2.0Hz), 7.04(1H,d,J=2.0Hz), 7.63(1H,brd,J=8.9Hz)

(7) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-Phe(4-F)-OH (650 mg, 2.05 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (0.62 g, 1.71 mmol) and CMPI (524 mg, 2.05 mmol) in THF (17 ml), TEA (0.57 ml, 4.10 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-



N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.05 g, 93%).

A mixture of the above compound (1.16 g, 1.75 mmol) and 10% palladium carbon (120 mg) in methanol (18 ml) was stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (761 mg, 82%).

EI-MS: 528(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.67, 0.80, 0.90, 0.92(6H, d, J=6.3-6.9Hz), 1.37, 1.39(9H, s), 2.21-3.22(6H, m), 2.61, 2.89(3H, s), 3.59-3.88, 4.34-4.48(3H, m), 5.33, 5.42(1H, brs), 5.90, 6.07(1H, brs), 6.56-7.18(7H, m), 8.71(1H, brd, J=8.3Hz)

#### Example 16

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (2.07 g, 4.63 mmol) in pyridine (46 ml), toluenesulfonyl chloride (6.79 g, 35.6 mmol) was added under cooling with ice. After stirring for 6.5 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was

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washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.46 g, 88%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.36(9H,s), 2.42(3H,s), 2.72-2.86(2H,m), 3.92-4.09(3H,m), 4.84-4.95(1H,m), 5.04(2H,s), 5.07(2H,s), 6.79(1H,d,J=8.0Hz), 6.87(1H,brd,J=8.0Hz), 7.06(1H,brs), 7.26-7.48(12H,m), 7.76(2H,d,J=8.3Hz)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester 2.4 g, 3.99 mmol) in ethanol (40 ml), a solution of sodium methanethiolate (560 mg, 7.99 mmol) in methanol (4 ml) was added and stirred at 40°C for 3 hours. The mixture was evaporated under reduced pressure to remove the solvent, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 5:1), giving the titled compound (1.63 g, 86%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.38(9H,s), 2.12(3H,s), 2.61(2H,d,J=5.6Hz), 2.85(2H,d,J=6.3Hz), 3.99-4.12(1H,m), 4.80-4.91(1H,m),

5.09(4H,s), 6.85(1H,d,J=8.3Hz), 6.96(1H,brd,J=7.6Hz),  
 7.11(1H,brs), 7.27-7.50(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester

5 To a solution of benzyl ester of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid (1.54 g, 3.23 mmol) in THF (75 ml) and water (25 ml), oxone (5.91 g, 6.46 mmol) was added at room temperature. After stirring for 1 hour, the mixture was mixed with water and extracted  
 10 with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl  
 15 acetate = 1:1), giving the titled compound (1.59 g, 97%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.38(9H,s), 2.88(3H,brs),  
 3.00(2H,brd,J=6.9Hz), 3.17(1H,dd,J=14.8,4.6Hz), 4.19-  
 4.30(1H,m), 4.35-4.47(1H,m), 5.07-5.18(1H,m), 5.09(2H,s),  
 5.10(2H,s), 6.85(1H,d,J=8.5Hz), 6.97(1H,dd,J=8.5,1.7Hz),  
 20 7.10(1H,brs), 7.28-7.49(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine

A mixture of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester (1.0 g, 1.96 mmol) and 20% palladium hydroxide/carbon (0.08 g) in  
 25 methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced

pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.56 g, 99%).

5  $^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.40(9H,s), 2.64(1H,dd,J=13.7,7.9Hz), 2.73(1H,dd,J=13.7,5.9Hz), 2.93-3.03(1H,m), 2.98(3H,s), 3.13(1H,dd,J=14.2,2.0), 3.61-3.74(1H,m), 6.62(1H,d,J=7.9Hz), 6.88(1H,dd,J=7.9,2.0), 7.05(1H,d,J=2.0Hz)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of Z-N-Me-Val-OH (518 mg, 1.96 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine (0.47 g, 1.63 mmol) and 15 CMPI (500 mg, 1.96 mmol) in THF (16 ml), TEA (0.55 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous 20 magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving the titled compound (0.70 g, 81%).

25  $^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.83(3H,d,J=6.6Hz), 0.89(3H,d,J=6.3Hz), 1.38(9H,s), 2.14-2.33(1H,m), 2.64-2.97(2H,m), 2.74(3H,s), 2.91(3H,s), 3.13(1H,dd,J=14.6,4.6Hz), 3.29(1H,dd,J=14.6,6.9Hz), 3.94(1H,d,J=11.2Hz), 4.43-

4.57(1H,m), 4.79(1H,brs), 5.14(2H,s), 6.40-6.84(3H,m),  
7.06(1H,brs), 7.37(5H,brs).

(6) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-  
N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-  
5 hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-  
methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-  
methanesulfonylmethylethylamide (0.65 g, 1.22 mmol) in  
methanol (10 ml), 10% palladium carbon (130 mg) was added  
10 and stirred in a hydrogen atmosphere at room temperature  
for 30 min. After filtration, the filtrate was  
concentrated under reduced pressure. To a solution of the  
thus obtained residue, Z-Phe(4-F)-OH (465 mg, 1.47 mmol)  
and CMPI (375 mg, 1.47 mmol) in THF (15 ml), TEA (0.41 ml,  
15 2.93 mmol) was added under cooling with ice and stirred at  
room temperature overnight. The reaction mixture was mixed  
with water and extracted with ethyl acetate. The organic  
layer was washed with saturated brine, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
20 under reduced pressure; the thus obtained residue was  
subjected to silica gel column chromatography (developing  
solvent:n-hexane: ethyl acetate =1:1) to give 2-((2-  
benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-  
methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-  
25 hydroxyphenyl)-1-methanesulfonylmethylethylamide (484 mg,  
57%). A mixture of the above compound (424 mg, 0.609 mmol)  
and 10% palladium carbon (43 mg) in methanol (16 ml) was  
stirred at room temperature in a hydrogen atmosphere for 2

hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol=15:1), giving the titled compound (239 mg, 70%).

EI-MS:563(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.65,0.78,0.91,0.93(6H,d,J=6.6-7.3Hz), 1.38, 1.39(9H,s), 2.22-2.40(1H,m), 2.46-3.40(6H,m), 2.66(3H,s), 2.93(3H,s), 3.60-3.83(1H,m), 3.87,4.26(1H,d,J=10.8Hz), 4.38-4.67(1H,m), 6.57-7.17,8.88(8H,m)

#### Example 17

Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

##### (1) Synthesis of 3-tBu-tyrosinol

To a solution of Z-3-tBu-tyrosinol (8.2 g, 23 mmol) in methanol (250 ml), 10% palladium carbon (800 mg) was added and stirred in a hydrogen atmosphere at room temperature for 10 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (5.1 g, 99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.40(9H,s), 2.45(1H,dd,J=8.6,13.5Hz), 2.71(1H,dd,5.3,13.5Hz), 3.0-3.2(1H,m), 3.38(1H,dd,J=7.6,10.5Hz), 3.65(1H,dd,J=3.6,10.5Hz), 6.61(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.06(1H,d,J=2.0Hz)

##### (2) Synthesis of (2-(benzyloxycarbonyl-N-methylamino)-3-

methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 3-tBu-tyrosinol (1 g, 4.48 mmol), Z-N-Me-Val-OH (1.43 g, 5.4 mmol) and CMPI (1.38 g, 5.4 mmol) in THF (45 ml), TEA (2.2 ml, 15.8 mmol) was added under  
5 cooling with ice and stirred at room temperature for 13 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced  
10 pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 90%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.84(3H,d,J=6.6Hz), 0.92(3H,d,J=6.3Hz),  
2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.5-3.7(2H,m), 3.9-4.2(2H,m),  
15 5.13(2H,s), 6.2-6.4(1H,m), 6.45(1H,d,J=7.6Hz),  
6.80(1H,brd,J=7.6Hz), 7.05(1H,brs), 7.36(5H,s)

(3) Synthesis of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

20 To a solution of (2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.9 g, 4 mmol) in methanol (40 ml), 10% palladium carbon (190 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. The  
25 reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.4 g).

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To a solution of the above crude compound (1.4 g), Boc-Phe(4-F)-OH (1.4 g, 4.94 mmol) and CMPI (1.3 g, 5.09 mmol) in THF (40 ml), TEA (2 ml, 14.3 mmol) was added under cooling with ice and stirred at room temperature for 12 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 78%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.77, 0.92, and 1.02(total 6H,d), 1.2-1.5(18H,m), 2.2-3.1(8H,m), 3.5-3.8(2H,m), 4.0-4.3, 4.4-4.5, 4.7-4.9, and 5.2-5.4(total 2H,m), 6.3-7.5(8H,m)

(4) Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (0.5 g) in methylene chloride (2 ml), TFA (2 ml) was added under cooling with ice, stirred for 1 hour at room temperature and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography



(developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (250 mg, 60%).

EI-MS:501(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.68, 0.79, and 0.93(total 6H,d,J=6.3-6.9Hz), 1.36 and 1.39(total 9H,s), 2.2-2.4(1H,s), 2.5-3.2(4H,m), 2.68 and 2.84(total 3H,s), 3.5-3.9(3H,m), 3.89 and 4.43(total 1H,d,J=10.9Hz), 4.0-4.4(1H,m), 6.5-7.1(7H,m), 6.58 and 8.41(total 1H,d,J=6.9-7.6Hz)

10 Example 18

(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

(1) Synthesis of (2-(2-(benzyloxycarbonylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (797 mg, 1.56 mmol) in methanol (15 ml), 10% palladium hydroxide (80 mg) was added and stirred at room temperature for 12 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (400 mg, 90%).

To a solution of the above crude compound (400 mg, 1.4 mmol), Z-Val-OH (528 mg, 2.1 mmol) and CMPI (539 mg, 2.1 mmol) in THF (10 ml), TEA (0.58 ml, 4.2 mmol) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (504 mg, 69%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.79(3H,d,J=6.9Hz), 0.91(3H,d,J=6.6Hz), 1.38(9H,s), 2.0-2.2(1H,m), 2.89(3H,s), 2.97(2H,d,J=6.9Hz), 3.1-3.4(2H,m), 3.94(1H,dd,J=5.6,7.9Hz), 4.4-4.6(1H,m), 5.10(2H,s), 5.1-5.2(1H,m), 5.35(1H,brs), 6.59(1H,d,J=8.3Hz), 6.5-6.7(1H,m), 6.88(1H,brd,J=8.3Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of of (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester

To a solution of Boc-Phe(4-F)-OH (1 g, 3.53 mmol) and O,N-dimethylhydroxylamine hydrochloride (0.38 g, 3.9 mmol) in methylene chloride (17 ml), TEA (1.1 ml, 7.9 mmol) and BOP (1.64 g, 3.7 mmol) were added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving N-methoxy-N-methyl-2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamide (1.08 g, 94%).

To a solution of the above compound (1 g, 3.07 mmol)

in ether (30 ml), lithium aluminum hydride (120 mg, 3.16 mmol) was added at -10°C and stirred at the same temperature for 10 min. The reaction mixture was mixed with 15 ml of a solution of potassium hydrogen sulfate (630 mg, 4.63 mmol). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (0.8 g, 98%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.44(9H,s), 3.0-3.2(2H,m), 4.3-4.5(1H,m), 5.02(1H,brs), 7.00(2H,t,J=8.6Hz), 7.13(2H,dd,J=5.4,8.6Hz), 9.63(1H,s)

(3) Synthesis of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(benzyloxycarbonylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (500 mg, 0.96 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(2-amino-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (330 mg).

To a solution of the above crude compound (330 mg, 0.86 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic



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anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (400 mg, 91%).

EI-MS: 535(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.75(3H, d, J=6.9Hz), 0.89(3H, d, J=6.9Hz), 1.39(9H, s), 2.0-2.1(1H, m), 2.3-2.5(2H, m), 2.53(1H, dd, J=3.6, 11.6Hz), 2.72(1H, dd, J=4.6, 13.2Hz), 2.80(1H, d, J=4.6Hz), 2.8-3.1(5H, m), 3.19(2H, d, J=5.9Hz), 4.5-4.7(1H, m), 6.62(1H, d, J=7.9Hz), 6.93(1H, dd, J=2.0, 7.9Hz), 6.99(2H, t, J=8.8Hz), 7.0-7.2(3H, m), 7.80(1H, d, J=8.6Hz)

#### Example 19

2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

(1) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylamino propionitrile

To a solution of Z-Phe(4-benzyloxy-3-tBu)-NH<sub>2</sub> (4.6 g, 10 mmol) in THF (20 ml), pyridine (1.6 ml, 20 mmol) and trifluoroacetic anhydride (1.55 ml, 11 mmol) were added under cooling with ice and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:4), giving the titled compound (3.35 g, 99%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.37(9H,s), 3.0(2H,m), 4.85(1H,brd),  
5.03(1H,brd), 5.10(2H,s), 5.14(2H,s), 6.69(1H,d,J=8.58Hz),  
7.05(1H,d,J=8.58Hz) 7.2(1H,s), 7.3-7.5(10H,m)

(2) Synthesis of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-  
5 benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone

A solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-  
benzyloxycarbonylamino propionitrile (3.48 g, 7.85 mmol) in  
saturated hydrochloric acid/ethanol (50 ml) was stirred at  
room temperature for 1.5 days. The reaction mixture was  
10 concentrated under reduced pressure and the thus obtained  
residue was dissolved in ethanol (70 ml); into the thus  
obtained solution, gaseous ammonia was blown under cooling  
with ice, followed by stirring at room temperature for 17  
hours. The resultant was concentrated under reduced  
15 pressure; the thus obtained residue was dissolved in  
methanol (50 ml), mixed with methyl acetoacetate (0.640 ml)  
and potassium hydroxide (562 mg) and stirred at room  
temperature for 4.5 days. The mixture was mixed with a  
saturated aqueous ammonium chloride solution and extracted  
20 with methylene chloride. The organic layer was dried over  
anhydrous magnesium sulfate, evaporated to remove the  
solvent under reduced pressure; the thus obtained residue  
was subjected to silica gel column chromatography  
(developing solvent: n-hexane:ethyl acetate = 2:1), giving  
25 the titled compound (1.76 g, 67%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.39(9H,s), 2.25(3H,s), 3.09(2H,brd),  
4.89(1H,brd), 5.03(2H,s), 5.07(2H,s), 5.80(1H,brd),  
6.14(1H,s), 6.79(1H,d,J=8.24Hz), 6.92(1H,d,J=8.24Hz),

6.96(1H,s), 7.25-7.43(10H,m)

(3) Synthesis of 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone

A suspension of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone (1.76 g, 3.35 mmol) and 20% palladium hydroxide/carbon (0.15 g) in methanol (30 ml) was stirred in a hydrogen atmosphere for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (824 mg, 82%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.37(9H,s), 2.32(3H,s), 2.74(1H,dd,J=8.90,9.24Hz), 3.15(1H,dd,J=4.28,4.29Hz), 4.09(1H,m), 6.16(1H,s), 6.59(1H,d,J=7.92Hz), 6.83(1H,d,J=7.92Hz), 6.99(1H,s).

(4) Synthesis of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

To a solution of Z-N-Me-Val-OH (678 mg, 2.55 mmol), 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone (700 mg, 2.32 mmol) and CMPI (653 mg, 2.55 mmol) in THF (20 ml), TEA (0.97 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove

the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (0.77 g, 61%).

5  $^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.79-0.90(6H,m), 1.30(9H,m), 2.2(4H,m), 2.8-3.1(5H,m), 4.3(1H,d,J=7.3), 4.97(1H,m), 5.1-5.25(2H,m), 6.18(1H,d,J=8.58), 6.41(1H,d,J=8.58Hz), 6.5-6.85(2H,m), 7.3(5H,m)

(5) Synthesis of 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone

A mixture of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (0.71 g, 1.294 mmol), 20% palladium hydroxide/carbon (0.15 g) and methanol (20 ml) was stirred in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving two diastereoisomers A and B of the titled compound, A (296 mg, 38%) being eluted first and then B (77 mg, 9.4%).

(A)

25  $^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.72(3H,d,J=6.93Hz), 0.83(3H,d,J=6.93Hz), 1.34(9H,s), 1.94(1H,m), 2.28(3H,s), 2.30(3H,s), 2.77(1H,d,J=4.62Hz), 3.11(2H,m), 5.04(1H,d,J=7.59Hz), 6.14(1H,s), 6.61(1H,d,J=7.92Hz), 6.81(1H,dd,J=7.92Hz), 6.99(1H,s), 7.84(1H,d,J=6.92Hz)



(B)

$^1\text{H-NMR}(\text{CDCl}_3)$ :  $\delta$  0.84(3H,d,J=6.93Hz), 0.89(3H,d,J=6.93Hz),  
1.33(9H,s), 2.00(1H,m), 2.14(3H,s), 2.18(3H,s),  
2.78(1H,d,J=4.95Hz), 3.11(2H,m), 5.10(1H,d,J=6.60Hz),  
5 6.14(1H,s), 6.63(1H,d,J=7.92Hz), 6.75(1H,dd,J=7.92Hz),  
6.97(1H,s), 7.81(1H,d,J=7.26Hz)

(6) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of Boc-Phe(4-F)-OH (200 mg, 0.707 mmol),  
2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (A)  
(244 mg, 0.589 mmol) and CMPI (180 mg, 0.706 mmol) in THF  
15 (8 ml), TEA (0.25 ml, 4.7 mmol) was added under cooling  
with ice and stirred at room temperature overnight. The  
reaction mixture was mixed with water and extracted with  
ethyl acetate. The organic layer was washed with saturated  
brine, dried over anhydrous magnesium sulfate and  
20 evaporated to remove the solvent under reduced pressure;  
the thus obtained residue was subjected to silica gel  
column chromatography (developing solvent: acetone:n-hexane  
= 1:2), giving the titled compound (0.33 g, 82%).

$^1\text{H-NMR}(\text{CDCl}_3)$ : (two rotamers)  $\delta$  0.75, 0.80 and  
25 0.98(6H,d,J=6.6,6.9Hz), 1.34 and 1.38(9H,s), 1.4 (9H,s),  
2.10(1H,m), 2.3 and 2.4(3H,s), 2.7(3H,s), 2.85(2H,m),  
3.04(2H,d,J=7.01Hz), 4.12 and 4.58(1H,d,J=9.6Hz),  
4.75(1H,m), 5.05(1H,m), 4.83 and 5.2(1H,brd), 5.45 and

5.6(1H,dd,J=7.4Hz), 6.2(1H,s), 6.6(1H,m), 6.77(1H,m),  
7.0(5H,m).

(7) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-  
fluorophenyl)propionyl)-N-methylamino)-3-methyl-  
5 butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-  
methyl-4-pyrimidinone (B)

To a solution of Boc-Phe(4-F)-OH (63 mg, 0.222 mmol),  
2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-  
methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (B)  
10 (77 mg, 0.185 mmol) and CMPI (57 mg, 0.222 mmol) in THF (5  
ml), TEA (0.08 ml, 0.573 mmol) was added under cooling with  
ice and stirred at room temperature overnight. The  
reaction mixture was mixed with water and extracted with  
ethyl acetate. The organic layer was washed with saturated  
15 brine, dried over anhydrous magnesium sulfate and  
evaporated to remove the solvent under reduced pressure;  
the thus obtained residue was subjected to silica gel  
column chromatography (developing solvent: acetone:n-hexane  
= 1:2), giving the titled compound (0.098 g, 74%).

20 <sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.78(6H,brd), 1.3-1.4(18H,s),  
1.8(2H,brd), 2.25(3H,brd), 2.8 and 3.20(7H,brd), 4.1(2H,m),  
4.4 and 4.5(1H,d,J=9.89Hz), 4.7 and 5.17(1H,brd), 5.3 and  
5.58(1H,d,J=9.89Hz), 6.0 and 6.17(1H,s), 6.6(1H,brd), 6.7-  
7.2(8H,m)

25 (8) Synthesis of 2-(1-(2-((2-amino-3-(4-  
fluorophenyl)propionyl)-N-methylamino)-3-methyl-  
butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-  
methyl-4-pyrimidinone (A)

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To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A) (279 mg) in methylene chloride (8 ml), TFA (1.3 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (225 mg, 95%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.7 and 0.8(6H,dd,J=6.6 and 6.59Hz), 1.29(9H,s), 2.14 and 2.275(3H,s), 2.1-2.2(1H,m), 2.67 and 2.78(3H,s), 2.6-2.8(2H,m), 3.07(2H,m), 3.7-3.83(1H,m), 4.15 and 4.62(1H,d,J=9.87Hz), 4.98 and 5.18(1H,dd,J=6.5 and 7.6Hz), 6.02 and 6.11(1H,s), 6.55 and 6.8(2H,m), 6.92(1H,d,J=6.92Hz), 6.93-7.15(4H,m)

(9) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B) (93 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1.5 hours and evaporated under reduced pressure to remove the

solvent; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (70 mg, 91.8%).

- 5  $^1\text{H-NMR}(\text{CDCl}_3)$ : (two rotamers)  $\delta$  0.68, 0.78 and 0.86(6H, dd,  $J=6.6$  and  $6.27\text{Hz}$ ), 1.3 and 1.32(9H, s), 2.21 and 2.23(3H, s), 2.2-2.4(1H, brd), 2.6 and 2.8(1H, m), 2.71-2.91(3H, s), 3.00(3H, m), 3.77 and 3.9(1H, m), 3.97 and 4.52(1H, d,  $J=9.37\text{Hz}$ ), 4.97 and 5.18(1H, m),
- 10 6.12(1H, d,  $J=3.3\text{Hz}$ ), 6.5-7.2(8H, m)

#### Example 20

- 5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
- 15

##### (1) Synthesis of Z-Tyr(3-tBu)-H

- To a solution of Z-Tyr(3-tBu)-OMe (3.30 g, 8.57 mmol) in THF (200 ml), diisobutyl aluminum hydride (1.0 M toluene solution) (42.9 ml, 42.9 mmol) was added dropwise at  $-78^\circ\text{C}$
- 20 over 15 min. After stirring for 1 hour, the mixture was mixed with methanol and a saturated aqueous  $\text{NaHCO}_3$  solution and extracted with ethyl acetate. The organic layer was washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the
- 25 solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.18 g, 72%).

NMR(CDCl<sub>3</sub>):δ 1.37(9H,s), 3.00-3.14(2H,m), 4.40-4.52(1H,m),  
4.89(1H,brs), 5.12(2H,s), 5.22-5.32(1H,m),  
6.57(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz), 7.00(1H,s), 7.30-  
7.42(5H,m), 9.64(1H,s)

5 (2) Synthesis of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-  
butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of Z-Tyr(3-tBu)-H (2.18 g, 6.14 mmol)  
in ethanol (25 ml), potassium cyanide (480 mg, 7.37 mmol),  
30% ammonium carbonate (1.77 g, 18.4 mmol) and water (25  
10 ml) were added and stirred at 60°C for 8 hours. The mixture  
was left for cooling and mixed with a saturated aqueous  
NaHCO<sub>3</sub> solution. The organic layer was extracted with ethyl  
acetate and washed with water and then with saturated brine,  
dried over anhydrous magnesium sulfate and evaporated to  
15 remove the solvent under reduced pressure; the thus  
obtained residue was subjected to silica gel column  
chromatography (developing solvent: ethyl acetate:n-hexane  
= 1:1), giving the titled compound (1.38 g, 53%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.37(9H,s), 2.90-3.00(2H,m), 3.10-  
20 3.22(1H,m), 4.27(1H,brs), 5.06(2H,s), 5.02-5.12(1H,m),  
6.07(1H,brs), 6.57(1H,d,J=8.2Hz), 6.88(1H,dd,J=2.0,8.2Hz),  
7.10(1H,d,J=2.0Hz), 7.22-7.40(5H,m)

(3) Synthesis of 5-(1-(2-(benzyloxycarbonyl-N-  
methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-  
25 hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(benzyloxycarbonylamino)-2-(3-  
tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione  
(543 mg, 1.28 mmol) in methanol (10 ml), 10% palladium

carbon (55 mg) was added and stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; to a solution of the thus obtained  
 5 residue in THF (13 ml), Z-N-Me-Val-OH (509 mg, 1.92 mmol), CMPI (491 mg, 1.92 mmol) and TEA (0.535 ml, 3.84 mmol) were added under cooling with ice and stirred at room temperature for 3 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic  
 10 layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving the titled  
 15 compound (365 mg, 53%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.79 and 0.85(6H,d,J=6.6Hz), 2.14-2.26(1H,m), 2.60(3H,s), 2.70-2.92(2H,m), 3.89(1H,d,J=10.8Hz), 4.27(1H,brs), 4.62-4.74(2H,m), 5.14(2H,s), 6.28(1H,d,J=7.9Hz), 6.56-7.10(3H,m), 7.30-  
 20 7.42(5H,m)

(4) Synthesis of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(benzyloxycarbonyl-N-  
 25 methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione (363 mg, 0.675 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen

atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (261 mg, 96%).

EI-MS:404(M<sup>+</sup>)

5 <sup>1</sup>H-NMR(DMSO-d<sub>6</sub>):δ 0.79 and 0.82(6H,d,J=6.3-6.6Hz), 1.31(9H,s), 1.90(3H,s), 2.74-2.84(2H,m), 4.02-4.14(1H,m), 4.17(1H,brs), 4.38-4.48(1H,m), 6.64(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz), 6.99(1H,s), 7.85(1H,brs)

(5) Synthesis of 5-(1-(2-(2-(benzyloxycarbonylamino)-3-(4-  
10 fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-  
15 hydroxylphenyl)ethyl)imidazolidine-2,4-dione (254 mg, 0.629 mmol) in THF (6 ml), Z-Phe(4-F)-OH (239 mg, 0.755 mmol), CMPI (193 mg, 0.755 mmol) and TEA (0.219 ml, 1.57 mmol) were added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed  
20 with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing  
25 solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (168 mg, 38%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.62,0.71,0.94 and 0.98(6H,d,J=6.0-6.6Hz), 1.34 and 1.37(9H,s), 2.26 and

2.92(3H,s), 2.24-2.42(1H,m), 2.64-3.12(4H,m), 3.84-  
4.32(2H,m), 4.50-4.82(2H,m), 5.02-5.12(2H,m), 5.20-  
5.64(1H,m), 6.21(1H,brs), 6.31(1H,brs), 6.50-6.60(2H,m),  
6.86-7.14(5H,m), 7.24-7.40(5H,m), 7.50-8.00(1H,m)

- 5 (6) Synthesis of 5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(2-(benzyloxycarbonylamino)-  
10 3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione (157 mg, 0.223 mmol) in methanol (5 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen  
15 atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to preparative TLC (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (83.0 mg, 65%).

- 20 FAB-MS: 570(M+H<sup>+</sup>)

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>): (two rotamers) δ 0.48-0.84(6H,m), 1.28, 1.32 and 1.33(9H,s), 2.00-2.12(1H,m), 2.28, 2.42 and 2.62(3H,s), 2.40-3.10(4H,m), 3.82-4.08(2H,m), 4.24-4.50(2H,m), 6.58-7.30(7H,m), 7.66-8.30(2H,m), 8.92-9.24(2H,m)

25

#### Example 21

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-



hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

(1) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester

To a solution of Z-Tyr(3-tBu)-OMe (4.0 g, 10.39 mmol) in ethanol (100 ml), hydrazine monohydrate (6.4 ml, 103.9 mmol) was added at room temperature. The mixture was stirred overnight and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with ethyl orthoformate (100 ml) and p-toluenesulfonic acid monohydrate (198 mg, 1.04 mmol) at room temperature. The mixture was stirred for 1.5 hours and mixed with 1N HCl (100 ml). The mixture was stirred for 20 min., and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.34 g, 33%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.32(9H,s), 3.19(2H,brs), 5.02(1H,brs), 5.05-5.16(2H,m), 5.35(2H,brs), 6.53(1H,d,J=7.9Hz), 6.75(1H,dd,J=7.9,2.0Hz), 6.85(1H,d,J=2.0Hz), 8.34(1H,s)

(2) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine

To a solution of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester (1.25 g, 3.16 mmol) in methanol (30 ml), 10% palladium carbon

(130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.80 g, 97%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.36(9H,s), 3.02(1H,dd,J=13.8,7.9Hz), 3.18(1H,dd,J=13.8,5.6Hz), 4.47(1H,dd,J=7.9,5.6Hz), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd,J=7.9,2.0Hz), 6.97(1H,d,J=2.0Hz), 8.40(1H,s)

(3) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-N-Me-Val-OH (914 mg, 3.45 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine (0.75 g, 2.87 mmol) and CMPI (881 mg, 3.45 mmol) in THF (30 ml), TEA (0.96 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving 2-benzyloxycarbonylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (1.28 g, 88%).

To a solution of the above compound (1.23 g) in

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methanol (24 ml), 10% palladium carbon (120 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus  
5 obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.87 g, 96%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.70(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz),  
10 1.35(9H,s), 1.88-2.03(1H,m), 2.34(3H,s), 2.77(1H,d,J=4.6Hz),  
3.12(1H,dd,J=14.0,8.4Hz), 3.28(1H,dd,J=14.0,5.9Hz),  
5.45(1H,brs), 5.61-5.71(1H,m), 6.58(1H,d,J=8.0Hz),  
6.68(1H,dd,J=8.0,2.0Hz), 6.96(1H,d,J=2.0Hz),  
7.84(1H,brd,J=8.9Hz), 8.35(1H,s)

15 (4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-Phe(4-F)-OH (835 mg, 2.63 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-  
20 hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (0.82 g, 2.19 mmol) and CMPI (672 mg, 2.63 mmol) in THF (22 ml), TEA (0.74 ml, 5.26 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl  
25 acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column

chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving 2-(2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)amino-N,3-dimethylbutyric acid 1-(1,3,4-oxadiazol-2-yl)-2-(3-t-butyl-4-hydroxyphenyl)ethylamide (1.31 g, 89%).

A mixture of the above compound (1.31 g, 1.95 mmol) and 10% palladium carbon (130 mg) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (752 mg, 72%).

EI-MS:539(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamer)δ 0.75, 0.78, 0.89, 0.92(6H,d,J=6.3-6.6Hz), 1.29,1.34(9H,s), 2.24-2.45(1H,m), 2.50-2.85(2H,m), 2.82(3H,s), 3.04-3.20(3H,m), 3.52-3.60,3.72-3.85(1H,m), 3.99,4.43(1H,d,J=10.9Hz), 5.42-5.53,5.64-5.73(1H,m), 6.42-7.18(7H,m), 8.33,8.42(1H,s), 9.62(1H,brd,J=9.2Hz)

#### Example 22

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

(1) Synthesis of N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Tyr(3-tBu)-OCH<sub>3</sub> (1.5 g, 5.97 mmol) in MeOH (10 ml), aqueous ammonia (10 ml) was added and

stirred at room temperature overnight. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving Tyr(3-tBu)-NH<sub>2</sub> (1.4 g, 99%).

To a solution of the thus obtained Tyr(3-tBu)-NH<sub>2</sub> (1 g, 4.23 mmol), Z-N-Me-Val-OH (1.23 g, 4.63 mmol) and CMPI (1.2 g, 4.69 mmol) in THF (20 ml), TEA (1.8 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving Z-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub> (1.7 g, 83%).

A mixture of the thus obtained Z-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub> (1.7 g), 20% palladium hydroxide/carbon (0.15 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (1.07 g, 88%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.67(3H, d, J=6.27Hz), 0.80(3H, d, J=6.6Hz),

1.35(9H,s), 1.91(1H,m), 2.25(3H,s), 2.76(1H,d,J=4.62Hz),  
3.00(2H,m), 4.75(1H,q,J=6.6Hz), 6.13(1H,s), 6.55(1H,s),  
6.66(1H,d,J=7.92Hz), 6.89(1H,d,J=7.59Hz), 7.02(1H,s),  
7.84(1H,d,J=7.91Hz)

5 (2) Synthesis of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Phe(4-F)-OH (890 mg, 3.14 mmol),  
N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub> (1 g, 2.86 mmol) and CMPI (804 mg,  
3.15 mmol) in THF (20 ml), TEA (1.2 ml, 7.16 mmol) was  
added under cooling with ice and stirred at room

10 temperature overnight. The reaction mixture was mixed with  
water and extracted with ethyl acetate. The organic layer  
was washed with saturated brine, dried over anhydrous  
magnesium sulfate and evaporated to remove the solvent  
under reduced pressure; the thus obtained residue was  
15 subjected to silica gel column chromatography (developing  
solvent: acetone:n-hexane = 1:2), giving Boc-Phe(4-F)-N-Me-  
Val-Tyr(3-tBu)-NH<sub>2</sub> (1.5 g, 85%).

(3) Synthesis of 2-((2-tertbutoxycarbonylamino-3-(4-  
fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid  
20 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-  
yl)ethylamide

A solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>  
(600 mg, 0.976 mmol) and N,N-dimethylacetamide (0.2 ml, 1.5  
mmol) in dioxane (3 ml) was stirred at room temperature for  
25 1 hour and mixed with a solution of sodium hydroxide (108  
mg) and hydroxylamine hydrochloride (190 mg) in acetic  
acid/water (7 ml/3 ml). The mixture was stirred at room  
temperature for 10 min., mixed with water and filtered; a

solution of the thus obtained precipitate in acetic acid/dioxane (10 ml/10 ml) was stirred at 60°C overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with

5 saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (474 mg, 76%).

10 <sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.76, 0.8, 0.86 and 0.98(6H,d,J=6.59,6.93,6.27,and 6.26Hz), 1.28 and 1.32(9H,s), 1.25 and 1.37(9H,s), 2.15(1H,m), 2.35 and 2.92(3H,s), 2.9(3H,m), 3.15(1H,d,J=6.93Hz), 4.12 and 4.49(1H,d,J=6.92Hz), 4.8(1H,m), 5.38 and 5.5(2H,m),  
15 6.65(1H,brd), 6.9-7.2 (7H,m), 8.37(1H,brd)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

To a solution of 2-((2-tertbutoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid  
20 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide (440 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated to  
25 remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (370

mg, 99%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):(two rotamers)δ 0.75 and 0.87 (total 6H,d and dd,J=6.59 and 6.92Hz), 1.27(9H,s), 2.17(1H,m), 2.77(2H,m), 2.83(3H,s), 3.1(2H,m), 3.55(1H,m), 3.96(1H,d,J=10.89Hz),  
5 5.7(1H,m), 6.45(1H,s), 6.59(1H,d, J=5.94Hz), 6.9(1H.brd),  
8.35(1H,s), 9.5(1H,d,J=8.91Hz), 6.95(2H,t,J=8.25Hz),  
7.06(2H,t,J=8.25Hz)

#### Example 23

10 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide

15 To a solution of Z-Tyr(3-tBu)-NH<sub>2</sub> (2.08 g, 5.62 mmol) in dioxane (70 ml), Lawesson's reagent (1.36 g, 3.37 mmol) was added and stirred at 80°C for 1 hour. The reaction mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to  
20 silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (1.66 g, 77%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.37(9H,s), 3.01-3.14(2H,m), 4.56-4.65(1H,m), 5.08(2H,s), 6.58(1H,d,J=7.9Hz),  
25 6.90(1H,dd,J=7.9,1.7Hz), 7.09(1H,d,J=1.7Hz), 7.20-7.40(5H,m)

(2) Synthesis of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine



To a solution of N-benzyloxycarbonyl-3-tBu  
tyrosinylthioamide (21.49 g, 55.67 mmol) in ethanol (300  
ml), bromoacetaldehyde diethylacetal (43 ml, 278 mmol) was  
added, stirred at 80°C for 2 hours, further mixed with  
5 bromoacetaldehyde diethylacetal (43 ml, 278 mmol), stirred  
at 80°C for 4 hours, further mixed with bromoacetaldehyde  
diethylacetal (43 ml, 278 mmol) and stirred at 80°C for 3  
hours. The mixture was evaporated to remove the solvent  
under reduced pressure and the thus obtained residue was  
10 subjected to silica gel column chromatography (developing  
solvent: ethyl acetate:n-hexane = 1:3), giving the titled  
compound (15.32 g, 67%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 1.29(9H,s), 3.10-3.30(2H,m), 5.10(2H,s),  
5.20-5.40(1H,m), 6.51(1H,d,J=8.3Hz), 6.74-6.78(2H,m), 7.22  
15 (1H,d,J=3.3Hz), 7.20-7.40(5H,brs), 7.76(1H,d,J=3.3Hz)

(3) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-1-  
(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-2-(3-tert-butyl-  
4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (15.28 g,  
20 37.27 mmol) in methylene chloride (1.1 l), thioanisole  
(8.75 ml, 74.54 mmol) was added. To the mixture, a  
solution of 1.0M boron tribromide in methylene chloride  
(186 ml, 186.34 mmol) was added dropwise under cooling with  
ice and stirred for 1 hour. The reaction mixture was mixed  
25 with water and alkalinized by 2N sodium hydroxide and  
extracted with methylene chloride. The organic layer was  
washed with saturated brine, dried over anhydrous magnesium  
sulfate and evaporated to remove the solvent under reduced

pressure, giving the titled compound (9.46 g, 90%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.36(9H,s), 2.82-3.27(2H,m), 4.51-  
4.56(1H,m), 6.57(1H,d,J=7.9Hz), 6.89(1H,dd,J=7.9,2.0Hz),  
6.99(1H,d,J=2.0Hz), 7.27(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

5 (4) Synthesis of 2-(N-tert-butoxycarbonyl-N-methylamino)-  
3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-  
(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-  
(thiazol-2-yl)ethylamine (4.67 g, 16.64 mmol), Boc-N-Me-  
10 Val-OH (5.0 g, 21.63 mmol) and CMPI (5.53 g, 21.63 mmol) in  
THF (110 ml), TEA (5.33 ml, 38.27 mmol) was added under  
cooling with ice and stirred at room temperature overnight.  
The reaction mixture was mixed with water and extracted  
with ethyl acetate. The organic layer was washed with  
15 saturated brine, dried over anhydrous magnesium sulfate and  
evaporated to remove the solvent under reduced pressure;  
the thus obtained residue was subjected to silica gel  
column chromatography (developing solvent: methanol:aqueous  
ammonia:methylene chloride = 3:0.1:100), giving the titled  
20 compound (8.10 g, 100%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.75-0.97(6H,m), 1.29(6H,s), 1.31(3H,s),  
1.41(3H,s), 1.48(6H,s), 2.10-2.35(1H,m), 2.71(1.5H,s),  
2.73(1.5H,s), 3.10-3.30(2H,m), 3.90-4.10(1H,m), 5.50-  
5.70(1H,m), 6.58(1H,d,J=7.9Hz), 6.70-6.90(2H,m),  
25 7.20(1H,d,J=3.0Hz), 7.74-7.76(1H,m)

(5) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-  
tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(N-tert-butoxycarbonyl-N-

methyldamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (8.03 g, 16.42 mmol) in methylene chloride (80 ml), TFA (40 ml) was added and stirred at room temperature for 30 min. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:hexane = 1:2), giving two diastereoisomers A and B of the titled compound, A (2.37 g, 37%) being eluted first and then B (2.17 g, 34%).

(A)

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.33(9H,s), 1.85-2.00(1H,m), 2.32(3H,s), 2.75(1H,d,J=4.6Hz), 3.09-3.37(2H,m), 5.63-5.71(1H,m), 6.61(1H,d,J=7.9Hz), 6.87-6.92(2H,m), 7.22(1H,d,J=3.0Hz), 7.77(1H,d,J=3.3Hz)

(B)

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.84(3H,d,J=6.9Hz), 0.92(3H,d,J=6.9Hz), 1.33(9H,s), 1.95-2.15(1H,m), 2.11(3H,s), 2.68(1H,d,J=5.0Hz), 3.12-3.39(2H,m), 5.60-5.69(1H,m), 6.59(1H,d,J=8.2Hz), 6.87(1H,dd,J=7.9,2.0Hz), 6.93(1H,d,J=2.0Hz), 7.22(1H,d,J=3.3Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methyldamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(A)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34 mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.55 g, 92%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.76(3H,d,J=6.6Hz), 0.86(2H,d,J=6.6Hz), 0.97(1H,d,J=6.6Hz), 1.26(3H,s), 1.29(6H,s), 1.37(6H,s), 1.40(3H,s), 2.15-2.40(1H,m), 2.70-3.50(4H,m), 2.78(3H,s), 4.17(0.3H,d,J=10.2Hz), 4.49(0.7H,d,J=11.2Hz), 4.70-4.85(1H,m), 5.25-5.80(1H,m), 6.58(1H,d,J=7.9Hz), 6.75-7.30(6H,m), 7.21(0.7H,d,J=3.3Hz), 7.23(0.3H,d,J=3.3Hz), 7.74(0.3H,d,J=3.3Hz), 7.77(0.7H,d,J=3.3Hz)

(7) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(B)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34

09890219 121201  
TOTAL 6722660

mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA  
(0.82 ml, 5.91 mmol) was added under cooling with ice and  
stirred at room temperature overnight. The reaction  
mixture was mixed with water and extracted with ethyl  
5 acetate. The organic layer was washed with saturated brine,  
dried over anhydrous magnesium sulfate and evaporated to  
remove the solvent under reduced pressure; the thus  
obtained residue was subjected to silica gel column  
chromatography (developing solvent: ethyl acetate:n-hexane  
10 = 1:2), giving the titled compound (1.54 g, 92%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.57(1H,d,J=6.6Hz), 0.62(1H,d,J=6.9Hz),  
0.78(4H,d,J=6.3Hz), 1.33(9H,s), 1.36(9H,s), 2.10-2.30(1H,m),  
2.60-3.70(4H,m), 2.82(1.8H,s), 2.85(1.2H,s),  
3.99(0.3H,d,J=10.6Hz), 4.51(0.7H,d,J=10.9Hz), 4.70-  
15 4.90(1H,m), 5.20-5.60(1H,m), 6.59-7.21(7H,m),  
7.20(1H,d,J=3.3Hz), 7.71(1H,d,J=3.3Hz)

(8) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-  
N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-  
hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

20 To a solution of 2-((2-butoxycarbonylamino-3-(4-  
fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid  
2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide  
(A) (1.49 g, 2.28 mmol) in methylene chloride (20 ml), TFA  
(10 ml) was added and stirred at room temperature for 1.5  
25 hours. The reaction mixture was evaporated to remove the  
solvent under reduced pressure; the thus obtained residue  
was mixed with methylene chloride, washed with a 2N aqueous  
sodium hydroxide solution and saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene

5 chloride = 3:0.1:100), giving the titled compound (430 mg).

EI-MS:554(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.75(2.3H,d,J=6.9Hz), 0.80(0.7H,d,J=6.6Hz), 0.90-0.92(0.7H,m), 0.93(2.3H,d,J=6.6Hz), 1.24(7H,s), 1.30(2H,s), 2.25-2.65(1H,m), 2.70-3.40(4H,m), 2.79(2.4H,s),  
10 2.85(0.6H,s), 3.50-3.60(0.8H,m), 3.75-3.90(0.2H,m), 3.97(0.8H,d,J=10.9Hz), 4.51(0.2H,d,J=10.6Hz), 5.45-5.60(0.2H,m), 5.65-5.80(0.8H,m), 6.55-7.20(7H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(9) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide  
20 (B) (1.48 g, 2.26 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous  
25 sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography

(developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (587 mg).

EI-MS:554(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.72(1.5H,d,J=6.9Hz), 0.786(1.5H,d,J=6.3Hz),  
 5 0.793(1.5H,d,J=6.6Hz), 0.88(1.5H,d,J=6.3Hz), 1.24(5.4H,s),  
 1.33(3.6H,s), 2.15-2.40(1H,m), 2.40-3.35(4H,m),  
 2.75(1.8H,s), 2.87(1.2H,s), 3.55-3.85(1H,m),  
 3.86(0.6H,d,J=10.9Hz), 4.56(0.4H,d,J=10.9Hz), 5.50-  
 5.65(1H,m), 6.45-7.15(7H,m), 7.17-7.20(1H,m),  
 10 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.0Hz)

#### Example 24

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid  
 15 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide

To a solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub> (400 mg, 0.651 mmol) in methylene chloride (6.5 ml), dimethylformamide dimethylacetal (0.26 ml, 1.954 mmol) was  
 20 added at room temperature. The mixture was stirred for 30 min. and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue in dioxane (6.5 ml), acetic acid (2 ml) and hydrazine monohydrate (48 μl, 0.977 mmol) were added at room  
 25 temperature. The mixture was stirred for 40 min., mixed with water and filtered to collect the precipitated solid. The thus obtained solid was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving

2-((2-t-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide (384 mg, 93%).

5 To a solution of the above compound (421 mg) in methylene chloride (3 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 30 min., mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl  
10 acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:  
15 chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (175 mg, 49%).

EI-MS:538(M<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.72, 0.87, 0.73-0.80(6H, d, J=6.3-6.6Hz), 1.22, 1.25(9H, s), 2.24-2.41(1H, m), 2.50-3.30(4H, m), 2.78,  
20 2.87(3H, s), 3.47-3.58, 3.79-3.88(1H, m), 4.00, 4.39(1H, brd, J=10.6Hz), 5.29-5.38, 5.40-5.50(1H, m), 6.41-7.11(7H, m), 7.52, 9.33(1H, brd, J=8.3Hz), 8.02, 8.10(1H, s)

#### Example 25

25 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of 2-tert-butoxycarbonylamino-3-



methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of Boc-Val-OH (890 mg, 4.09 mmol), 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine  
5 (1.03 g, 3.73 mmol) and CMPI (653 mg, 1.05 mmol) in THF (10 ml), TEA (1 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine,  
10 dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.88 g, 99%).

15 <sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.79 and 0.89(6H,d,J=6.93Hz), 1.29 and 1.31(9H,s), 1.42 and 1.44(9H,s), 2.15(1H,brd), 3.23(2H,m), 3.89(1H,m), 5.0(1H,brd), 5.4(0.7H, brd), 5.57(1H,q,J=6.93 and 5.92Hz), 6.56(1H,q,J=4.62 and 4.29Hz), 6.8(3H,brd), 7.21(1H,m), 7.75(1H,t,J=2.07 and 3.3Hz)

20 (2) Synthesis of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.7 g) in methylene chloride (14 ml), TFA (6 ml) was added under cooling with ice and  
25 stirred at room temperature for 2 hours. The mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene

chloride:methanol:ethyl acetate = 20:1:2), giving two diastereoisomers A and B of the titled compound, A (700 mg) being eluted first and then B (650 mg, 99%).

(A)

5  $^1\text{H-NMR}(\text{CDCl}_3\text{-CD}_3\text{OD})$ :  $\delta$  0.89(6H, brd), 1.28(9H, s), 2.15(1H, m), 3.18-3.7(3H, m), 5.48(1H, brd), 6.6(1H, brd), 6.8(2H, brd), 7.27(1H, s), 7.7(1H, s)

(B)

10  $^1\text{H-NMR}(\text{CDCl}_3\text{-CD}_3\text{OD})$ :  $\delta$  0.72(6H, d,  $J=6.27\text{Hz}$ ), 1.31(9H, s), 1.92(1H, brd), 3.04(2H, brd), 3.28(1H, dd,  $J=5.28$  and  $5.6\text{Hz}$ ), 5.55(1H, m), 6.62(1H, d,  $J=7.92\text{Hz}$ ), 6.86(1H, brd), 6.97(1H, s), 7.28(1H, s), 7.68(1H, d,  $J=2.64\text{Hz}$ )

(3) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (600 mg, 1.59 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml),  $\text{NaBH}_3\text{CN}$  (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled

compound (935 mg, 93%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.75 and 0.83(6H,d,J=6.93 and 6.59Hz),  
1.36(9H,s), 1.42(9H,s), 2.46(2H,brd), 2.66(2H,brd),  
2.73(1H,d, J=4.61Hz), 2.81(1H,d, J=7.26Hz),  
5 3.20(2H,d,J=6.26Hz), 3.6(2H,m), 3.8(1H,brd), 4.7(1H,brd),  
5.6(1H,q,J=6.93 and 5.94Hz), 6.61(1H,d,J=7.92Hz),  
6.77(1H,s), 6.85(1H,d,J=7.92Hz), 6.9-7.21(8H,m),  
7.66(1H,d,J=2.97Hz)

(4) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-  
10 fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-  
butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-amino-3-methylbutyric acid 2-(3-  
tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)  
(600 mg, 1.59 mmol) and 1-formyl-2-(4-  
15 fluorophenyl)ethyl carbamic acid tBu ester (640 mg, 2.39  
mmol) in MeOH (10 ml),  $\text{NaBH}_3\text{CN}$  (200 mg, 3.1 mmol) was added  
under cooling with ice and stirred at room temperature for  
one hour. The mixture was evaporated under reduced  
pressure, mixed with water and extracted with ethyl acetate.  
20 The organic layer was washed with saturated brine, dried  
over sodium sulfate and evaporated to remove the solvent  
under reduced pressure; the thus obtained residue was  
subjected to silica gel column chromatography (developing  
solvent: ethyl acetate:n-hexane = 1:1), giving the titled  
25 compound (950 mg, 95%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  0.83 and 0.87(6H,d,J=6.93 and 6.92Hz),  
1.34(9H,s), 1.41(9H,s), 2.00(1H,brd), 2.31(2H,brd), 2.6-  
2.81(3H,brd), 2.81(1H,d, J=7.26Hz), 3.20(2H,m), 3.6(2H,m),

3.8(1H,brd), 4.58(1H,brd), 4.83(1H,brd),  
5.59(2H,q,J=6.93Hz), 6.60(1H,d,J=7.92Hz),  
6.81(1H,d,J=7.91Hz), 6.88(1H,s), 6.9-7.21(8H,m),  
7.74(1H,d,J=2.29Hz)

- 5 (5) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (300  
10 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica  
15 gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (180 mg, 71%).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>):δ 0.78 and 0.88(6H,d,J=3.3 and 5.6Hz),  
1.28(9H,s), 1.90(1H,brd), 2.6(1H,m), 2.7-3.0(3H,brd),  
20 3.1(2H,m), 3.4(1H,brd), 5.29(1H,q,J=5.93 and 8.58Hz),  
6.69(1H,d,J=7.92Hz), 6.86(1H,d,J=7.59Hz), 6.95(1H,s),  
7.2(4H,m), 7.62(1H,d,J=2.97Hz), 7.77(1H,d,J=3.3Hz)

- (6) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)  
25

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (300

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mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (193 mg, 76%).

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>):δ 0.61(6H,q,J=6.6 and 12.54Hz), 1.3(9H,s), 1.72(1H,s), 2.7-3.0(4H,brd), 3.16(1H,s), 3.28(1H,m), 3.5(1H,brd), 5.37(1H,m), 6.65(1H,d,J=8.25Hz), 6.85(1H,d,J=10.89Hz), 7.0(1H,s), 7.2(4H,m), 7.68(1H,d,J=2.97Hz), 7.81(1H,d,J=3.3Hz)

#### Example 26

15 Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Tyr(2-F)-OH (0.60 g, 3.01 mmol) and di-tert-butyl dicarbonate (0.69 g, 3.16 mmol) in dioxane/water (5 ml/5 ml), TEA (0.84 ml, 6.02 mmol) was added under cooling with ice and stirred for 2 hours. The reaction mixture was concentrated to approximately a half volume, mixed with a saturated aqueous NaHCO<sub>3</sub> solution and washed with ether. The aqueous layer was rendered acidic by the addition of 2N hydrochloric acid under cooling with ice, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Boc-Tyr(2-F)-OH (0.85 g).

To a solution of the above crude Boc-Tyr(2-F)-OH (0.82 g), N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.77 g, 2.11 mmol) and CMPI (0.81 g, 3.17 mmol) in THF (5 ml), TEA (1.18 ml, 8.44 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.21 g, 15%).

(2) Synthesis of Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.21 g, 0.326 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous NaHCO<sub>3</sub> solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (173 mg, 82%).

EI-MS(M<sup>+</sup>):544

<sup>1</sup>H-NMR(DMSO-d<sub>6</sub>-CDCl<sub>3</sub>):δ 0.21(6/5H,d,J=6.3Hz), 0.59(6/5H,d,J=6.6Hz), 0.71(9/5H,d,J=6.6Hz), 0.84-0.98(9/5H,m), 1.30(27/5H,s), 1.37(18/5H,s), 2.00-2.22(1H,m), 2.10(6/5H,s), 2.3-2.8(2H,m), 2.44(9/5H,s),

2.85(9/5H,d,J=5.9Hz), 3.1-3.8(2H,m), 3.24(6/5H,d,J=5.0Hz),  
3.94-4.20(1H,m), 4.51(2/5H,d,J=10.2Hz),  
4.78(2/5H,dd,J=3.9,11.2Hz), 4.88(3/5H,d,J=10.2Hz),  
5.41(3/5H,dd,J=3.9,10.2Hz), 6.48-7.21(7.7H,m), 7.60-  
5 7.75(0.3H,m), 8.88(1H,d,J=7.3Hz), 9.47(1H,brs)

#### Example 27

Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

(1) Synthesis of Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

10 To a solution of Tyr(3-F)-OH (0.80 g, 4.02 mmol) and  
di-tert-butyl dicarbonate (0.92 g, 4.22 mmol) in  
dioxane/water (7 ml/7 ml), TEA (1.12 ml, 8.04 mmol) was  
added under cooling with ice and stirred for 2.5 hours.  
The reaction mixture was concentrated to approximately a  
15 half volume, mixed with a saturated aqueous NaHCO<sub>3</sub> solution  
and washed with ether. The aqueous layer was rendered  
acidic by the addition of 2N hydrochloric acid under  
cooling with ice, and extracted with chloroform. The  
organic layer was dried over anhydrous magnesium sulfate  
20 and evaporated to remove the solvent under reduced pressure,  
giving crude Boc-Tyr(3-F)-OH (1.18 g).

To a solution of the above crude Boc-Tyr(3-F)-OH  
(1.18 g), N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (1.10 g, 3.03 mmol)  
and CMPI (1.16 g, 4.55 mmol) in THF (6 ml), TEA (1.27 ml,  
25 12.1 mmol) was added under cooling with ice and stirred at  
room temperature for 27 hours. The reaction mixture was  
mixed with water, and extracted with ethyl acetate. The  
organic layer was washed with saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.19 g, 10%).

(2) Synthesis of Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

To a solution of Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> (0.19 g, 0.294 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous NaHCO<sub>3</sub> solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (136 mg, 85%).

EI-MS(M<sup>+</sup>):544

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>-CDCl<sub>3</sub>):δ 0.18(6/5H,d,J=6.3Hz), 0.58(6/5H,d,J=6.6Hz), 0.68(9/5H,d,J=6.6Hz), 0.85(9/5H,d,J=6.3Hz), 1.29(27/5H,s), 1.37(18/5H,s), 1.95-2.21(1H,m), 2.04(6/5H,s), 2.30-3.00(2H,m), 2.41(9/5H,s), 2.81(9/5H,s), 3.10-3.60(16/5H,m), 3.55-6.64(3/5H,m), 4.00-4.10(2/5H,m), 4.45(2/5H,d,J=10.2Hz), 4.70(2/5H,dd,J=3.9,11.2Hz), 4.85(3/5H,d,J=10.2Hz), 5.38(3/5H,dd,J=3.9,10.2Hz), 6.51-7.31(8H,m), 8.98(1H,d,J=2.6Hz), 9.50(1H,brs)

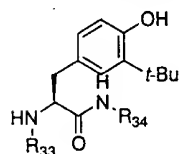
Examples 28-64 were conducted according to Scheme 1



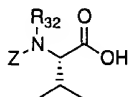
and Examples 65-78 were conducted according to Scheme 2.  
 The following Reference Examples show the methods of  
 preparing Intermediates of Schemes 1 and 2. Table C-1  
 shows structural formulae of Intermediates of Examples 28-  
 5 64.

Table C-1

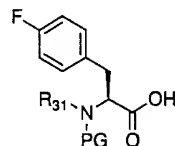
Intermediates of Examples 28-78



T 1 : R33=R34=H  
 T 2 : R33=H, R34=Me  
 T 4 : R33=Me, R34=H (Example 1 (5))  
 T 5 : R33=R34=Me  
 T 7 : R33=Et, R34=H  
 T 8 : R33=Et, R34=Me  
 T 1 7 : R33=Me, R34=CH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>  
 T 1 8 : R33=H, R34=tBu

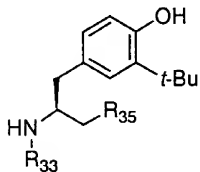


V1: R32=Me (Commercial)  
 V2: R32=Et

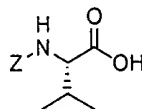


P1: PG=Boc, R31=H (Commercial)  
 P2: PG=Boc, R31=Me  
 P3: PG=Z, R31=Et  
 P10: PG=Boc, R31=Et

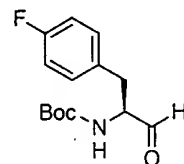
10



T19: R33=H, R35=OH (Example 17)  
 T20: R33=Me, R35=H  
 T21: R33=R35=H  
 T22: R33=H, R35=NH(Boc) (Example 10)  
 T23: R33=Me, R35=OH



V4 (Commercial)



P 1 1

In Table C-1, "(Example 1 (5))", "(Example 17)" and  
 "(Example 10)" mean that the methods of preparing the  
 compounds are described in the corresponding Examples 1 (5),  
 15 17 and 10, respectively. "Commercial" means that the  
 compound is commercially available.

Reference Example 1

Synthesis of Intermediate T1

A mixture of Tyr(3-tBu)-OMe (12.4 g, 49 mmol) and concentrated aqueous ammonia (240 ml) was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (CHCl<sub>3</sub>:MeOH = 10:1), giving Tyr(3-tBu)-NH<sub>2</sub> (T1) (10 g, 80%).  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.40(9H, s), 2.63(1H, dd, J=9.6, 13.9Hz), 3.19(1H, dd, J=4.0, 13.9Hz), 3.58(1H, dd, J=4.0, 9.6Hz), 5.11(1H, brs), 5.38(1H, brs), 6.64(1H, d, J=7.9Hz), 6.92(1H, dd, J=2.0, 7.9Hz), 7.11(1H, d, J=2.0Hz).

Reference Example 2

Synthesis of Intermediate T2

A mixture of Tyr(3-tBu)-OMe (12 g, 48 mmol) and a 40% methylamine methanol solution (80 ml) was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure, giving Tyr(3-tBu)-NHMe (T2) (12 g) as a crude product.

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.39(9H, s), 2.60(1H, dd, J=9.6, 13.9Hz), 2.83(3H, d, J=5.0Hz), 3.18(1H, dd, J=4.0, 13.9Hz), 3.57(1H, dd, J=4.0, 9.6Hz), 6.67(1H, d, J=7.9Hz), 6.88(1H, dd, J=1.8, 7.9Hz), 7.07(1H, d, J=1.8Hz).

Reference Example 3

Synthesis of Intermediate T5

(1) Synthesis of N-formyl-Tyr(3-tBu)-OMe

To a solution of acetyl chloride (22.6 ml, 299 mmol) in diethyl ether (1 l), sodium formate (30.6 g, 450 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was  
5 filtered and evaporated to remove the solvent. The thus obtained residue was added dropwise to a solution of H-Tyr(3-tBu)-OMe (22.2 g, 83.8 mmol) in methylene chloride (500 ml) under cooling with ice, mixed with TEA (46.7 ml, 335 mmol) and stirred at room temperature for 2 hours. The  
10 reaction mixture was mixed with saturated aqueous NaHCO<sub>3</sub> and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to  
15 silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving N-formyl-Tyr(3-tBu)-OMe (23.8 g, 100%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 1.38(9H,s), 3.09(2H,d,J=5.3Hz), 3.76(3H,s), 4.93(1H,dd,J=5.3,13.5Hz), 5.23(1H,s), 6.02(1H,d,J=13.5Hz),  
20 6.55(1H,d,J=7.9Hz), 6.80(1H,dd,J=2.0,7.9Hz), 6.95(1H,d,J=2.0Hz), 8.18(1H,s).

#### (2) Synthesis of N-Me-Tyr(3-tBu)-OMe

To a solution of N-formyl-Tyr(3-tBu)-OMe (23.8 g, 85.3 mmol) in THF (400 ml), 1.0M borane-THF complex (170  
25 ml) was added dropwise under cooling with ice over 30 min. The mixture was stirred for 20 min., mixed with methanol (50 ml) and further stirred for 30 min. The reaction mixture was mixed with 33% hydrobromic acid/acetic acid (31

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ml) and stirred for 2 hours. The mixture was neutralized by saturated aqueous  $\text{NaHCO}_3$  under cooling with ice and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium

5 sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me-Tyr(3-tBu)-OMe (20.3 g, 90%).

10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): $\delta$  1.38(9H,s), 2.37(3H,s), 2.89(2H,d,J=6.6Hz), 3.42(1H,t,J=6.6Hz), 3.68(3H,s), 6.55(1H,d,J=7.9Hz), 6.86(1H,dd,J=2.0,7.9Hz), 7.02(1H,d,J=2.0Hz)

#### (3) Synthesis of N-Me-Tyr(3-tBu)-NHMe

To a solution of N-Me-Tyr(3-tBu)-OMe (8.20 g, 31.1 mmol) in methanol (20 ml), a 30% methylamine methanol solution (200 ml) was added and stirred at room temperature for 16 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column

15 chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me-Tyr(3-tBu)-NHMe (T5) (6.27 g, 76%).

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): $\delta$  1.39(9H,s), 2.26(3H,s), 2.58(1H,dd,J=10.5,14.8Hz), 2.84(2H,d,J=4.9Hz), 3.06- 3.18(2H,m), 5.00(1H,brs), 6.62(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 7.08(1H,d,J=1.7Hz), 7.15(1H,brs).

Reference Example 4

Synthesis of Intermediate T7

A mixture of Tyr(3-tBu)-NH<sub>2</sub> (1.6 g, 6.8 mmol) and acetaldehyde (7.6 ml, 0.14mol) was stirred under cooling with ice for 10 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (34 ml) and then under cooling with ice with sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (CHCl<sub>3</sub>:MeOH = 20:1), giving N-Et-Tyr(3-tBu)-NH<sub>2</sub> (T7) (1.3 g, 73%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.96(3H,t,J=7.3Hz), 1.40(9H,s), 2.4-2.7(3H,m), 3.14(1H,dd,J=4.0,13.9Hz), 3.26(1H,dd,J=4.0,9.6Hz), 5.25(1H,s), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.10(1H,d,J=2.0Hz), 7.18(1H,brs).

20

Reference Example 5

Synthesis of Intermediate T8

A mixture of Tyr(3-tBu)-NHMe (1.7 g, 6.8 mmol), acetaldehyde (0.76 ml, 13.6 mmol) and dichloromethane (10 ml) was stirred under cooling with ice for 30 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (20 ml) and then under cooling with ice with

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sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated under reduced pressure under cooling with ice; the thus obtained residue was subjected to silica gel column chromatography (CHCl<sub>3</sub>:MeOH=20:1), giving N-Et- Tyr(3-tBu)-NHMe (T8) (1.7 g, 90%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.94(3H,t,J=7.3Hz), 1.39(9H,s), 2.4-2.6(2H,m), 2.60(1H,dd,J=9.6,13.8Hz), 2.83(3H,d,J=4.9Hz), 3.13(1H,dd,J=4.0,13.8Hz), 3.25(1H,dd,J=4.0,9.6Hz), 5.44(1H,brs), 6.64(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.07(1H,d,J=2.0Hz), 7.27(1H,brs)

15 Reference Example 6

Synthesis of Intermediate V2

To a solution of Z-Val-OH (50 g) in THF (500 ml), ethyl iodide (127.3 ml, 1592 mmol) was added under cooling with ice and then sodium hydride (60% in oil) (23.88 g, 597 mmol) was added slowly, followed by stirring at 60°C for 12 hours. The reaction mixture was mixed with water and washed with ether. The thus obtained aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The resultant was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (H:EA:AcOH = 100:50:1),



THF/DMF (73 ml/37 ml), ethyl iodide (28.1 ml, 352 mmol) and 60% sodium hydride (5.28 g, 132 mmol) were added under cooling with ice and stirred at room temperature for 5.5 hours. Water was added slowly to the reaction mixture, followed by washing with ether. The aqueous layer was adjusted to pH 3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:acetic acid = 100:50:1), giving Z-N-Et-Phe(4-F)-OH (P3) (10.9 g, 72%).

#### Reference Example 9

#### 15 Synthesis of Intermediate P10

To a solution of Boc-Phe(4-F)-OH (1.0 g, 3.53 mmol) in THF/DMF (6 ml/1.5 ml), ethyl iodide (2.24 ml, 20.8 mmol) and 60% sodium hydride (422 mg, 10.6 mmol) were added under cooling with ice and stirred at room temperature for 19 hours. The reaction mixture was mixed with water slowly and then with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution and extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:15), giving Boc-N-Et-Phe(4-F)-OH (P10) (593 mg, 54%).



Reference Example 10

Synthesis of Intermediate T17

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A suspension of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH<sub>2</sub> (2.5 g, 5.27 mmol), a 35% aqueous formaldehyde solution (10 ml) and potassium carbonate (2.19 g, 15.8 mmol) in acetonitrile was stirred for 2 hours. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous NH<sub>4</sub>Cl solution and then with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:1), giving Z-N-Me-Phe(3-tBu-4-benzyloxy)-NHCH<sub>2</sub>OH (2.0 g).

To a solution of the above compound (2.0 g, 3.97 mmol) in 85% formic acid (30 ml), sodium methanesulfinate (1.5 g, 15.3 mmol) was added and then stirred at 50°C for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; to a solution of the thus obtained residue (1.8 g) in methanol (20 ml), 20% palladium hydroxide/carbon (0.50g) was added and stirred in a hydrogen atmosphere for 2 days. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:methanol:methylene chloride

=1:1:15), giving N-Me-Phe(3-tBu-4-benzyloxy)-NHCH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>,  
(T17) (890 mg).

#### Reference Example 11

#### 5 Synthesis of Intermediate T18

To a solution of Z-Tyr(3-tBu)-OMe (1.01 g, 2.62 mmol)  
in methanol/water (12 ml/3 ml), lithium hydroxide  
monohydrate (0.17 g, 3.93 mmol) was added and stirred at  
room temperature for 2 hours. The reaction mixture was  
10 washed with ether, rendered acidic by 2N hydrochloric acid  
and extracted with methylene chloride. The extract was  
dried over anhydrous magnesium sulfate and evaporated to  
remove the solvent under reduced pressure, giving crude Z-  
Tyr(3-tBu)-OH (0.98 g).

15 To a solution of the above crude compound (0.92 g,  
2.48 mmol), WSCI (0.52 g, 2.73 mmol) and HOBt (0.37 g, 2.73  
mmol) in DMF (15 ml), tert-butylamine (0.31 ml, 2.48 mmol)  
and then NMM (0.29 ml, 2.73 mmol) were added under cooling  
with ice and stirred at room temperature for 2 hours. The  
20 reaction mixture was mixed with water, and extracted with  
ethyl acetate. The organic layer was washed with 2N  
hydrochloric acid, a saturated aqueous NaHCO<sub>3</sub> solution and  
saturated brine in that order. The extract was dried over  
anhydrous magnesium sulfate and concentrated under reduced  
25 pressure; the thus obtained residue was subjected to silica  
gel column chromatography (ethyl acetate:n-hexane = 1:2),  
giving Z-Tyr(3-tBu)-NHtBu (1.05 g, 99%).

To a solution of the above compound (1.0 g, 2.34

mmol) in methanol (20 ml), 20% palladium hydroxide/carbon (0.16 g) was added and stirred in a hydrogen atmosphere for 2 hours. The reaction mixture was filtered with Celite and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude Tyr(3-tBu)-NHtBu (T18) (0.60 g, 88%).

#### Reference Example 12

##### Synthesis of Intermediate T20

- 10 (1) Synthesis of 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (27.8 g, 58.5 mmol) in THF (290 ml), ethyl chloroformate (6.2 ml, 64.3 mmol) and N-methyl morpholine 7.7 ml, 70.2 mmol) were added under cooling with ice and stirred. After 2 hours, the reaction mixture was mixed with sodium borohydride (6.7 g, 175 mmol), water (100 ml) and methanol (100 ml) and stirred at room temperature for 6 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:1:2), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-1-hydroxymethyl-N-methylethylamine (12.4 g, 46%).

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A solution of the above compound (5.21 g, 11.2 mmol) in methylene chloride (55 ml), TEA (2.34 ml, 16.8 mmol) and methanesulfonyl chloride (0.954 ml, 12.3 mmol) were added under cooling with ice and stirred for 30 min. Under  
5 cooling with ice, the reaction mixture was mixed with saturated aqueous NaHCO<sub>3</sub> and extracted with methylene chloride. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure,  
10 giving a mesylate. To a solution of the mesylate in THF (30 ml), a 1M lithium triethyl borohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 1 hour, further lithium triethylborohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 30 min., the mixture was mixed with  
15 water under cooling with ice and extracted with chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column  
20 chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine (3.42 g, 68%).  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.14(3H,d,J=6.9Hz), 1.36(9H,s), 2.50-2.80(2H,m), 2.76 and 2.83(total 3H,s), 4.30-4.58(1H,m),  
25 4.88-5.10(4H,m), 6.74-7.14(3H,m), 7.20-7.50(10H,m)

(2) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-N-methyl-1-methylethylamine (T20)

A suspension of 2-(4-benzyloxy-3-tert-butylphenyl)-N-





methylethylamine

A suspension of N-benzyl-2-(4-benzyloxy-3-tert-butylphenyl)-1-methyl-N-(benzyloxycarbonyl)-ethylamine (2.35 g, 4.50 mmol) and 20% palladium hydroxide/carbon catalyst (0.50 g) in methanol (30 ml) was stirred in a hydrogen atmosphere overnight. The mixture was filtered to remove the catalyst and the filtrate was evaporated to remove the solvent under reduced pressure, giving 2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethylamine (T21) (0.90 g, 96%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$  1.16(3H,d,J=6.6Hz), 1.39(9H,s), 2.45(1H,dd,J=4.9, 13.3Hz), 2.69(1H,dd,J=4.9,13.3Hz), 3.15(1H,m), 3.52H,brs), 6.58(1H,d,J=7.9Hz), 6.83(1H,dd,J=1.6,7.9Hz), 7.03(1H,d,J=1.6Hz).

#### Reference Example 14

#### Synthesis of Intermediate T23

To a solution of Tyr(3-tBu)-OMe (3.0 g, 11.9 mmol) in 1,4-dioxane/water (12 ml/12 ml), sodium carbonate (1.9 g, 17.9 mmol) and then ethyl chlorocarbonate (1.26 ml, 13.1 mmol) were added under cooling with ice and stirred for 2 hours. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue (3.85 g) in THF (120 ml), lithium aluminum hydride (2.83 g, 59.7 mmol) was added little by little and stirred at 60°C for 5 hours. The reaction mixture was poured into ice water,





6.98(1H,d,J=8.9Hz), 7.11(1H,d,J=8.2Hz), 7.13(1H,d,J=8.2Hz).

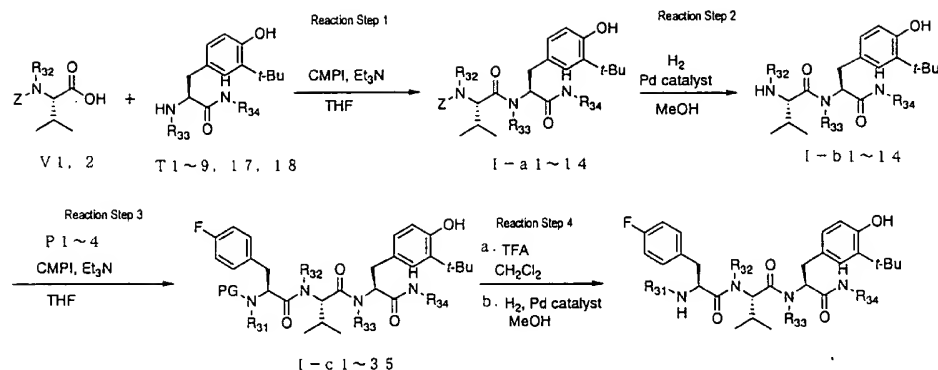
(2) Synthesis of 2-(4-fluorophenyl)-1-formylethylcarbamic acid tert-butyl ester (P11)

To a solution of the above compound (3.30 g, 10.1  
5 mmol) in diethyl ether (150 ml), lithium aluminum hydride  
(498 mg, 13.1 mmol) was added under cooling with ice and  
stirred for 30 min. The reaction mixture was mixed with a  
solution of potassium hydrogen sulfate (2.75 g, 20.2 mmol)  
in water (20 ml) and stirred for 1 hour. The reaction  
10 mixture was filtered and extracted with ethyl acetate. The  
organic layer was washed with saturated brine, dried over  
anhydrous magnesium sulfate and evaporated to remove the  
solvent under reduced pressure. The thus obtained residue  
was subjected to silica gel column chromatography  
15 (developing solvent: ethyl acetate:n-hexane = 1:5), giving  
the titled compound (2.37 g, 88%).

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 1.44(9H,s), 3.00-3.20(2H,m), 4.34-  
4.46(1H,m), 4.98-5.06(1H,m), 6.98(1H,d,J=8.6Hz),  
7.01(1H,d,J=8.6Hz), 7.12(1H,d,J=8.3Hz), 7.14(1H,d,J=8.3Hz),  
20 9.63(1H,s).

Scheme 1 shows the synthesis scheme of Examples 28-64.

Scheme 1: synthesis scheme of Examples 28-64



Synthesis process shown in scheme 1 is explained below:

#### 5 Reaction step 1

To a solution of Compounds T and V and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a.

#### Reaction step 2

To a solution of Compound I-a in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b.

#### Reaction step 3

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To a solution of Compounds I-b and P and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed  
5 with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c.

10 Reaction step 4a (PG=Boc)

To a solution of Compound I-c in methylene chloride, TFA was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous  $\text{NaHCO}_3$  solution  
15 and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

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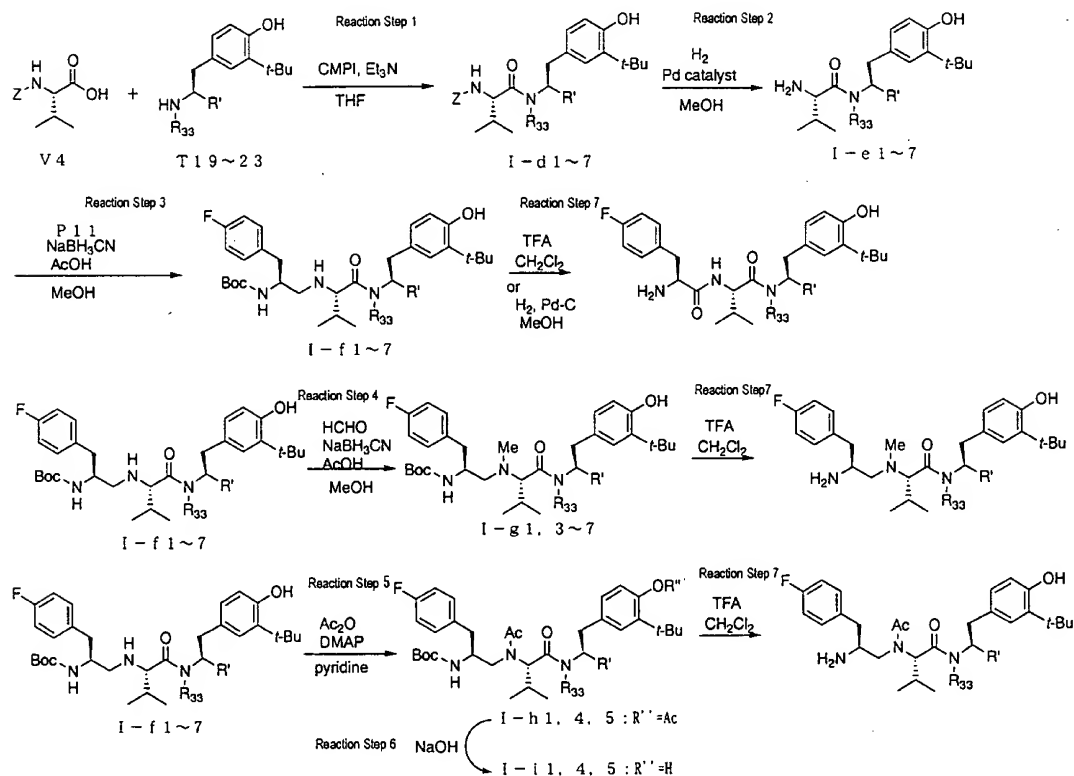
Reaction step 4b (PG=Z)

To a solution of Compound I-c in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove  
25 the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Scheme 2 shows the synthesis scheme of Examples 65-78.

Scheme 2: synthesis scheme of Examples 65-78

5



Synthesis process shown in scheme 2 is explained

10 below:

#### Reaction step 1

To a solution of Compounds T and V4 and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and  
 15 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium

sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-d.

#### Reaction step 2

5           To a solution of Compound I-d in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium catalyst and the filtrate was evaporated to remove the solvent under reduced pressure. The thus  
10           obtained residue was subjected to silica gel column chromatography, giving Compound I-e.

#### Reaction step 3

            To a solution of Compounds P11 and I-e in methanol, acetic acid and sodium cyanoborohydride were added under  
15           cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous  $\text{NaHCO}_3$  and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced  
20           pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-f.

#### Reaction step 4

            To a solution of Compound I-f in methanol, 35% aqueous formaldehyde solution, acetic acid and sodium  
25           cyanoborohydride were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous  $\text{NaHCO}_3$  and extracted with chloroform. The organic layer was washed with saturated

brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-g.

5 Reaction step 5

To a solution of Compound I-f in pyridine, acetic acid anhydride and 4-dimethylaminopyridine were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous copper sulfate solution, water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-h.

Reaction step 6

To a solution of Compound I-h in methanol, a 2N aqueous sodium hydroxide solution was added and stirred at room temperature. The reaction mixture was mixed with saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-i.

Reaction step 7

To a solution of Compound I-f, or I-g, or I-i in methylene chloride, TFA was added and stirred at room

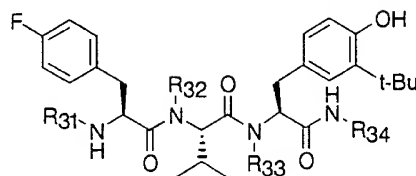
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temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous  $\text{NaHCO}_3$  solution and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and  
5 evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Examples conducted according to Scheme 1 are shown in Tables D-1 to D-43.

Table D-1

## Structural Formula of Compounds of Example 28-64



## Example 28

5 Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>			R <sub>33</sub>		R <sub>34</sub>	
H		Me			H		H	
Reaction 1								
Compound Tl:g	Compound Vl:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.35	1.3	2.1	40	19	EA:H 3:1	I-a1	1.6
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.84 and 0.88(6H,d,J=6.6Hz), 1.36(9H,s), 2.15-2.35(1H,m), 2.75(3H,s), 2.8-3.1(2H,m), 4.02(1H,brd,J=11.2Hz), 4.5-4.7(1H,m), 5.13 and 5.15(2H,s), 5.3-5.5, 5.5-5.7, 5.8-6.0, 6.1-6.2, and 6.5-6.8(3H,m), 6.45(1H,d,J=7.9Hz), 6.81(1H,brd,J=7.9Hz), 7.07(1H,brs), 7.37(5H,s)								
Reaction 2								
Compound I-a1:g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time hr		Column sol.		Product	Amount g
1.5	0.3	30	1		Not purified		I-b1	1.1
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.37(9H,s), 1.8-2.0(1H,m), 2.30(3H,s), 2.74(1H,d,J=4.3Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.3-5.7(1H,m), 6.1-6.3(1H,m), 6.5-6.7(1H,m), 6.93(1H,brd,J=7.9Hz), 7.06(1H,brs), 7.6-7.8(1H,m)								

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Table D-2

Example 28(Continued from Table D-1)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>

Reaction 3								
Compound I-b1:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.3	0.29	0.26	0.43	5	18	MC:M 20:1	I-cl	0.45
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.77, 0.89, and 1.01(6H,d,J=6.6Hz), 1.33, 1.36, 1.37, and 1.39(18H,s), 2.15-2.4(1H,m), 2.32 and 2.77(3H,s), 2.7-3.0(4H,m), 4.1-4.3, 4.5-4.6, and 4.6-4.8(2H,m), 5.36(1H,brd,J=8.9Hz), 5.44, 5.57, 5.71, 5.75, and 6.18(3H,brs), 6.6-7.2(7H,m), 7.8-7.9(1H,m)								

Reaction 4a						
Compound I-cl:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.4	2	4	0.5	CH:M:N 400:10:1	0.32	17.8

EI-MS(M <sup>+</sup> ):514						
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.71, 0.79, 0.91, and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.38(9H,s), 2.2-2.4(1H,m), 2.4-3.2(4H,m), 2.70 and 2.83(3H,s), 3.56 and 3.79(1H,dd,J=5.0-5.9,7.6Hz), 3.94 and 4.44(1H,d,J=10.9-11.2Hz), 4.56 and 4.74(1H,dd,J=6.6-8.9,14.2-16.2Hz), 5.47(1H,brs), 5.85 and 5.96(1H,brs), 6.4-6.9(3H,m), 6.9-7.2(5H,m), 9.01(1H,d,J=7.9Hz)						

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Table D-3

## Example 29

Synthesis of N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Me		Me		H		H	
Reaction 3							
Compound I-b1:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction Time hr	Column sol.	Product Amount g
0.3	0.31	0.26	0.43	5	20	MC:M 20:1	I-C2 0.43
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.72, 0.79, and 0.92(6H, d, J=6.6Hz), 1.33, 1.34, 1.37, and 1.40(18H, s), 2.1-2.3(1H, m), 2.24 and 2.67(3H, s), 2.6-3.3(4H, m), 4.40 and 4.50(1H, d, J=10.9-11.6Hz), 4.5-4.8(1H, m), 4.8-4.9 and 5.0-5.2(1H, m), 5.49 and 5.98(2H, brs), 6.16(1H, s), 6.31(1H, brd, J=8.3Hz), 6.5-6.8(2H, m), 6.8-7.3(5H, m)							
Reaction 4a							
Compound I-c2:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction Time hr	Column sol.	Amount g	HPLC min	
0.35	1.5	3	0.5	CH:M:N 400:10:1	0.24	18.0	
EI-MS(M <sup>+</sup> ):528							
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.52, 0.79, and 0.91(6H, d, J=5.0-6.9Hz), 1.33 and 1.39(9H, s), 2.1-2.3(1H, m), 2.24 and 2.36(3H, s), 2.56 and 2.61(3H, s), 2.6-3.2(4H, m), 3.54 and 3.61(1H, dd, J=5.9-6.3, 7.3-7.6Hz), 3.78 and 4.58(1H, d, J=10.9Hz), 4.49 and 4.68(1H, dd, J=7.3, 14.5Hz), 5.38, 5.58, 5.78, and 5.90(2H, brs), 6.6-7.2(7H, m), 9.07(1H, brd, J=7.6Hz)							

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Table D-4

## Example 30

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Et		Me		H		H	
Reaction 3							
Compound I-b1:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.3	0.36	0.26	0.43	5	16	CH:M:N 400:10:1	I-c3 0.42
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.41, 0.67, and 0.86(6H,d,J=6.6Hz), 1.0-1.2(3H,m), 1.36(9H,s), 2.1-2.3(1H,m), 2.51 and 2.76(3H,s), 2.6-3.0 and 3.0-3.2(6H,m), 4.1-4.3(1H,m), 4.4-4.6(1H,m), 4.9-5.0 and 5.1-5.3(1H,m), 5.13(2H,s), 5.35(1H,brs), 5.76(2H,brs), 6.1-6.2 and 6.4-7.4(13H,m)							
Reaction 4a							
Compound I-c3:g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.37	0.07	5	1	CH:M:N 400:10:1	0.24	18.5	
EI-MS(M <sup>+</sup> ):542							
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.39, 0.77, and 0.90(6H,d,J=6.3-6.9Hz), 1.05 and 1.16(3H,t,J=6.9Hz), 1.32 and 1.39(9H,s), 2.1-2.3(1H,m), 2.3-3.2(6H,m), 2.43 and 2.46(3H,s), 3.5-3.7(1H,m), 3.76 and 4.58(1H,d,J=10.9-11.5Hz), 4.47 and 4.68(1H,dd,J=7.0,13.9Hz), 5.42, 5.73, and 6.00(2H,brs), 6.6-7.2(7.8H,m), 8.74(0.2H,d,J=7.9Hz)							

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Table D-5

## Example 31

## Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Me		H		Me		
Reaction 1								
Compound T2:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.07	1.36	1.31	1.79	43	2.5	EA:H 1:1	I-a2	2.11
EI-MS(M <sup>+</sup> ):497								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.84 and 0.89(6H,d,J=6.6Hz), 1.36(9H,s), 2.12-2.30(1H,m), 2.71, 2.73, and 2.74(6H,s), 2.70-3.00(2H,m), 4.04(1H,d,J=11.2Hz), 4.40-4.58(1H,m), 4.82-4.86(1H,m), 5.19(2H,s), 5.70-5.80(1H,m), 6.43(1H,d,J=7.9Hz), 6.53(1H,d,J=8.2Hz), 6.80(1H,d,J=8.2Hz), 7.04(1H,s), 7.30-7.42(5H,m)								
Reaction 2								
Compound I-a2:g	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.01	200	50	2	C:M 20:1	I-b2	1.43		
EI-MS(M <sup>+</sup> ):363								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.67 and 0.83(6H,d,J=5.9Hz), 1.37(9H,s), 1.84-2.02(1H,m), 2.31(3H,s), 2.73(1H,d,J=5.9Hz), 2.74(3H,d,J=5.0Hz), 2.90-3.08(2H,m), 4.52(1H,ddd,J=7.2,7.2,7.2Hz), 5.51(1H,brs), 5.98(1H,d,J=3.6Hz), 6.61(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.04(1H,d,J=2.0Hz), 7.68(1H,d,J=7.9Hz)								

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Table D-6

Example 31(Continued from Table D-5)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

Reaction 3								
Compound I-b2:mg	Compound P1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
400	387	337	0.46	11	13	EA:H 2:1	I-c4	652
EI-MS(M <sup>+</sup> ):628								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.75, 0.77, 0.88, and 1.00(total 6H,d,J=5.3-6.3Hz), 1.36, 1.37 and 1.39(total 18H,s), 2.16-2.30(1H,m), 2.72(3H,d,J=4.6Hz), 2.70-3.22(7H,m), 4.38-4.80, and 5.10-5.22(total 3H,m), 5.28 and 5.32(total 1H,brs), 5.54-5.64(1H,m), 6.04-6.12(1H,m), 6.58-7.22(7H,m)								
Reaction 4a								
Compound I-c4:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
564	2	8	1.5	MC:M 20:1	367	18.9		
EI-MS(M <sup>+</sup> ):528								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.72,0.81 and 0.92(total 6H,d,J=6.3-6.6Hz), 1.36 and 1.38(total 9H,s), 2.20-2.40(1H,m), 2.50-3.24(10H,m), 3.59(2/3H,dd,J=5.6,7.6Hz), 3.73(1/5H,d,J=7.0Hz), 3.80(1/3H,dd,J=6.0,8.3Hz), 3.95(4/5H,d,J=8.9Hz), 4.40-4.54(2/5H,m), 4.63(3/5H,dd,J=6.6,14.2Hz), 5.65 and 5.78(total 1H,d,J=3.8-4.3Hz), 6.60(1/4H,d,J=8.3Hz), 6.70-7.16(7H,m), 9.07(3/4H,d,J=8.3Hz)								

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Table D-8

## Example 33

## Synthesis of N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Et		Me		H		Me		
Reaction 3								
Compound I-b2:mg	Compound P3:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
490	559	414	0.45	8	13	EA:H 1:1	I-c6	747
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.40, 0.47, 0.67 and 0.86(total 6H,d,J=6.3-6.9Hz), 1.06-1.22(3H,m), 1.36 and 1.38(total 9H,s), 2.10-2.26(1H,m), 2.49 and 2.78(total 3H,s), 2.79 and 2.73(total 3H,d,J=4.6-4.9Hz), 2.60-3.40(6H,m), 4.28-4.44(2H,m), 4.90-5.16(3H,m), 5.40-5.68(2H,m), 6.38-7.42(12H,m)								
Reaction 4b								
Compound I-c6:mg	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
660	66	10	12	CH:M:N 10:1:0.1	184	19.6		
EI-MS(M <sup>+</sup> ):556								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.40, 0.77 and 0.89(total 6H,d,J=6.6Hz), 1.06 and 1.19(total 3H,t,J=7.0-7.3Hz), 1.34 and 1.38(total 9H,s), 2.10-2.28(1H,m), 2.48(3H,s), 2.30-3.20(6H,m), 2.73 and 2.74(total 3H,d,J=4.6Hz), 3.58-3.70(1H,m), 3.76(3/10H,d,J=11.2Hz), 4.38(7/10H,dt,J=4.9,7.3Hz), 4.50(7/10H,d,J=11.2Hz), 4.56(3/10H,dt,J=7.3,7.9Hz), 5.72-5.90(2/3H,m), 6.60-7.18(8H,m), 8.68(1/2H,d,J=7.9Hz)								

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Table D-9

## Example 34

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>					
Me	Me	Me	H					
Reaction 3								
CompoundI I-b3:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.600	0.638	0.549	0.46	16	16	H:EA=2:1	I-c7	0.729
Reaction 4a								
Compound I-c7:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.635	3.00	15	2	MC:M:H 10:1:1	0.413	19.6		
EI-MS(M <sup>+</sup> ):542								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.58, 0.81, 0.82 and 0.93(6H, d, J=6.4-6.9 Hz), 1.32 and 1.40(9H, s), 2.20-2.34(1H, m), 2.22 and 2.24(3H, s), 2.50 and 2.93(3H, s), 2.84 and 3.04(3H, s), 2.52 and 2.74(3H, d, J=6.5-6.9Hz), 3.18-3.41(1H, m), 3.42 and 3.62(1H, t, J=5.0-6.8Hz), 5.03 and 5.13(1H, d, J=10.7-10.9 Hz), 5.42-5.49(1H, m), 5.38 and 6.01(1H, brs), 6.38 and 6.62(1H, d, J=8.0Hz), 6.78-6.99(3H, m), 7.04-7.12(3H, m)								

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Table D-10

## Example 35

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Et		Me		Me		H	
Reaction 3							
Compound I-b3:g	Compound P4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.460	0.520	0.420	0.53	10.0	17	H:EA 2:1	I-c8 0.300
Reaction 4a							
Compound I-c8:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.300	1.44	1.44	2	MC:M:H 10:1:1	0.200	20.2	
EI-MS(M <sup>+</sup> ):556							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.54~1.1(6H, m and d, J=6.3Hz), 1.35 and 1.39(9H, s), 2.48 and 2.81(3H,s) 2.97 and 3.07(3H, s), 2.21 ~ 3.76(7H, m), 5.55~5.02(3H,m), 6.37 and 6.61(1H, d, J=8.3Hz), 6.78~7.21(6H, m)							

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### Example 36

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Table D-12

## Example 37

## Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH-Me

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Me		Me		Me		Me	
Reaction 3							
CompoundI I-b4:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product  Amount g
0.430	0.440	0.400	0.47	10.00	19	EA:H:MC 2:1:1	I-c10 0.500
Reaction 4a							
Compound I-c10:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.500	2.50	2.50	1	MC:M:H 15:1:2	0.260	20.3	
EI-MS(M <sup>+</sup> ):556							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.76~0.92(6H, m and d, J=6.3Hz), 1.34 and 1.39(9H, s), 2.25(3H, d, J=11.6Hz), 2.52 and 2.82(3H, s), 2.95 and 3.07(3H, s), 2.21 ~ 3.64(5H, m), 2.71 and 2.76(3H, d, J=4.3Hz), 5.42~5.01(3H,m), 6.37 and 6.54(1H, d, J=8.2Hz), 6.78~7.11(6H, m)							

Ergonomics		Ergonomics	
Task	Time (s)	Task	Time (s)
1. Preparing the test	10.0	1. Preparing the test	10.0
2. Setting up the test	10.0	2. Setting up the test	10.0
3. Running the test	10.0	3. Running the test	10.0
4. Collecting data	10.0	4. Collecting data	10.0
5. Analyzing data	10.0	5. Analyzing data	10.0
6. Reporting results	10.0	6. Reporting results	10.0
7. Cleaning up	10.0	7. Cleaning up	10.0
8. Total	80.0	8. Total	80.0

Ergonomics		Ergonomics	
Task	Time (s)	Task	Time (s)
1. Preparing the test	10.0	1. Preparing the test	10.0
2. Setting up the test	10.0	2. Setting up the test	10.0
3. Running the test	10.0	3. Running the test	10.0
4. Collecting data	10.0	4. Collecting data	10.0
5. Analyzing data	10.0	5. Analyzing data	10.0
6. Reporting results	10.0	6. Reporting results	10.0
7. Cleaning up	10.0	7. Cleaning up	10.0
8. Total	80.0	8. Total	80.0

Ergonomics		Ergonomics	
Task	Time (s)	Task	Time (s)
1. Preparing the test	10.0	1. Preparing the test	10.0
2. Setting up the test	10.0	2. Setting up the test	10.0
3. Running the test	10.0	3. Running the test	10.0
4. Collecting data	10.0	4. Collecting data	10.0
5. Analyzing data	10.0	5. Analyzing data	10.0
6. Reporting results	10.0	6. Reporting results	10.0
7. Cleaning up	10.0	7. Cleaning up	10.0
8. Total	80.0	8. Total	80.0

Ergonomics		Ergonomics	
Task	Time (s)	Task	Time (s)
1. Preparing the test	10.0	1. Preparing the test	10.0
2. Setting up the test	10.0	2. Setting up the test	10.0
3. Running the test	10.0	3. Running the test	10.0
4. Collecting data	10.0	4. Collecting data	10.0
5. Analyzing data	10.0	5. Analyzing data	10.0
6. Reporting results	10.0	6. Reporting results	10.0
7. Cleaning up	10.0	7. Cleaning up	10.0
8. Total	80.0	8. Total	80.0

Table D-14

## Example 39

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
H		Me		Et		H	
Reaction 1							
Compound T7:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
4.000	5.720	5.510	6.02	100	24	EA:H:MC 2:1:1	I-a5 3.310
Reaction 2							
Compound I-a5 :g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr	Column sol.	Product Amount g		
3.100	0.300	70.00	1	MC:M:H 15:1:2	I-b5 1.600		
Reaction 3							
Compound d I-b5:g	Compound d P1:g	CMPI g	TEA ml	THF ml	Reactio n time hr	Column sol.	Produc t Amount g
0.400	0.430	0.370	0.46	10.00	19	EA:H:MC 2:1:1	I-c12 0.380
Reaction 4a							
Compound I-c12:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.380	1.50	1.50	2	MC:M:H 15:1:2	0.150	20.5	
EI-MS(M <sup>+</sup> ):542							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.72~1.33(m, 9H), 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz), 2.70 and 2.90(3H, s), 2.21 ~ 3.70 (7H, m) 4.92~5.23(3H, m), 6.41 and 6.61(1H, d, J=7.9Hz), 6.80~7.19(6H, m)							

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R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>
Me	Me	Et	H

Reaction 3

Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.440	0.450	0.380	0.48	10.00	19	EA:H:MC 2:1:1	I-c13	0.220

Reaction 4a

Compound I-c13:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.220	1.50	1.50	2	MC:M:H 15:1:2	0.130	21.0

EI-MS(M<sup>+</sup>):447

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): (two rotamers) δ 0.72~0.95(6H, d, J=6.6Hz), 1.13~1.32(3H, m) 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz) 2.21 ~ 3.96 (7H, m), 2.75 and 3.08 (3H, s), 4.92~5.40(3H, m), 6.41 and 6.63(1H, d, J=7.9Hz), 6.78~7.19(6H, m)

Table D-16

## Example 41

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Et		Me		Et		H	
Reaction 3							
Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.490	0.480	0.420	0.52	10.00	19	EA:H:MC 2:1:1	I-c14 0.260
Reaction 4a							
Compound I-c14:g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.260	0.030	10.00	2	MC:M:H 15:1:2	0.120	21.9	
EI-MS(M <sup>+</sup> ):570							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.74~1.26(12H, m ), 1.34 and 1.39(9H, s), 2.84 and 2.67(3H, s), 2.22~3.81(8H, m), 4.7~5.22(3H, m), 6.43 and 6.59(1H, d, J=7.9Hz), 6.81~7.19(6H, m)							

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Table D-17

## Example 42

## Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Me		Et		Me		
Reaction 1								
Compound T8:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.20	4.80	4.62	6.31	75	13	EA:H 1:1	I-a6	4.33
EI-MS(M <sup>+</sup> ):585								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.53, 0.80, 0.82 and 0.89(total 6H,d,J=6.3-6.6Hz), 0.96-1.30(3H,m), 1.34,1.36 and 1.36(total 9H,s), 2.20-2.40(1H,m), 2.46 and 2.75(total 3H,d,J=4.6Hz), 2.57 and 2.95(total 3H,s), 2.66-3.68(4H,m), 4.33, 4.45 and 4.59(total 1H,d,J=10.6Hz), 4.78-4.92(1H,m), 4.96-5.36(3H,m), 6.30-7.12(4H,m), 7.30-7.44(5H,m)								
Reaction 2								
Compound I-a6:g	Pd(OH) <sub>2</sub> mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.81	280	60	1.5	CH:M 10:1	I-b6	2.10		
EI-MS(M <sup>+</sup> ):391								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.34, 0.73, 0.90 and 0.96(total 6H,d,J=6.3-6.9Hz), 1.13 and 1.18(total 3H,t,J=6.9Hz), 1.36 and 1.37(total 9H,s), 1.60-1.80(1/2H,m), 2.14 and 2.27(total 3H,s), 2.10-2.30(1/2H,m), 2.58(1/2H,d,J=9.6Hz), 2.92-3.64(9/2H,m), 4.50-4.60(1/3H,m), 4.96-5.10(2/3H,m), 5.10-5.30(1H,m), 6.48(2/3H,brs), 6.54(1/3H,d,J=7.9Hz), 6.57(2/3H,d,J=7.9Hz), 6.79(1/3H,dd,J=2.0,7.9Hz), 6.91(2/3H,dd,J=2.0,7.9Hz), 7.00(1/3H,d,J=2.0Hz), 7.10(2/3H,d,J=2.0Hz), 8.24-8.34(1/3H,m)								

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Table D-18

Example 42(Continued from Table D-17)

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

Reaction 3								
Compound I-b6:mg	Compoun dP1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
457	397	359	0.39	6	22	MC:M 20:1	I-c15	724
EI-MS(M <sup>+</sup> ):657								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.72,0.78,0.82 and 0.89(total 6H,d,J=6.3-6.9Hz),1.08 and 1.16(total 3H,t,J=6.9Hz),1.33,1.36,1.38,and 1.39(total 18H,s),2.14-2.28(1H,m),2.54 and 2.98(total 3H,s),2.65 and 2.75(total 3H,d,J=4.6-4.9Hz),2.60-3.64(6H,m),4.58-5.18(4H,m),6.32-6.72(2H,m),6.90-7.18(5H,m)								
Reaction 4a								
Compound I-c15:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
651	3	7	1	MC:M:H 20:1:1	354	21.5		
EI-MS(M <sup>+</sup> ):556								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.67,0.82 and 0.92(total 6H,d,J=6.6Hz),1.10 and 1.15(total 3H,t,J=6.9Hz),1.34 and 1.39(total 9H,s),2.24-2.44(1H,m),2.67 and 2.76(total 3H,d,J=4.3-4.9Hz),2.73 and 3.05(total 3H,s),2.50-3.90(7H,m),4.94-5.08(2H,m),6.36-7.18(7H,m)								

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Table D-19

## Example 43

## Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Me		Me		Et		Me		
Reaction 3								
Compound I-b6:mg	Compound P2:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
465	424	365	0.40	6	21	EA:H 2:1	I-c16	759
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.45, 0.73, 0.82 and 0.89(total 6H,d,J=6.4-6.9Hz), 1.02(3H,t,J=6.6Hz), 1.29, 1.36, 1.37, 1.39 and 1.42(total 18H,s), 2.20-2.30(1H,m), 2.36, 2.71, 2.93 and 3.67(total 6H,s), 2.77 and 2.90(total 3H,d,J=4.6-4.9Hz), 2.60-3.44(6H,m), 4.80-5.28(total 3H,m), 6.09(1H,d,J=4.0Hz), 6.19 and 6.35(total 1H,dd,J=1.3,7.3Hz), 6.51(1/2H,s), 6.60 and 6.69(total 1H,d,J=7.3Hz), 6.94-7.16(13/2H,m)								
Reaction 4a								
Compound I-c16:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr		Column sol.	Amount mg	HPLC min	
651	3	7	1		MC:M:H:N 10:1:1:0.1	457	22.1	
EI-MS(M <sup>+</sup> ):570								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.72, 0.83 and 0.92(total 6H,d,J=6.6Hz), 1.14 and 1.16(total 3H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.23 and 2.27(total 3H,s), 2.20-2.40(1H,m), 2.55(1H,d,J=6.3Hz), 2.64-2.88(7H,m), 2.99(1H,dd,J=9.2,14.9Hz), 3.23(1H,dd,J=6.9,14.9Hz), 3.40-3.74(3H,m), 5.00-5.12(2H,m), 6.40 and 6.57(total 1H,d,J=7.9-8.2Hz), 6.44(1/2H,brs), 6.80(1/2H,dd,J=1.6,7.9Hz), 6.90-7.18(11/2H,m)								

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Table D-20

## Example 44

## Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Et		Me		Et		Me		
Reaction 3								
Compound I-b6:mg	Compound P3:mg	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
640	675	501	0.55	9	17	EA:H 1:1	I-c 17	963
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.71, 0.78, 0.88, 1.07 and 1.09(total 6H,d,J=6.3-6.9Hz), 0.98 and 1.18(total 3H,t,J=6.9Hz), 1.29, 1.35 and 1.39(total 9H,s), 2.14-2.30(1H,m), 2.48-3.56(14H,m), 4.78(1H,d,J=10.6Hz), 4.86-5.24(3H,m), 5.98-6.10(3/2H,m), 6.21(1H,s), 6.59 and 6.64(total 1H,d,J=7.9Hz), 6.84-7.20(11/2H,m), 7.30-7.44(5H,m)								
Reaction 4b								
Compound I-c17:mg	Pd(OH) <sub>2</sub> mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
870	87	15	15	CH:M 10:1	252	22.9		
EI-MS(M <sup>+</sup> ):584								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.73, 0.82 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.01, 1.06, 1.13 and 1.16(total 6H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.20-3.04(5H,m), 2.67 and 2.78(total 3H,s), 2.69 and 2.74(total 3H,d,J=4.6-4.9Hz), 3.26(1H,dd,J=7.9,14.2Hz), 3.45(1H,dd,J=8.9,13.2Hz), 3.54-3.74(2H,m), 4.94-5.12(5/2H,m), 5.38-5.46(1/2H,m), 6.42 and 6.57(total 1H,d,J=7.9-8.3Hz), 6.80-7.16(6H,m)								

FOI 67205250

Table D-21

## Example 45

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Et		H		H		
Reaction 1								
Compound T1:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.3	4.29	4.0	4.3	80	2	EA:H 3:1	I-a7	6.5
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.7-1.0(9H,m), 1.2-1.4(9H,m), 2.2-2.4(1H,m), 2.8-3.0(1H,m), 3.0-3.15(1H,m), 3.2-3.35(2H,m), 3.6-3.7(1H,brd,J=10.9Hz), 4.45-4.6(1H,m), 5.04(1H,brs), 5.15(1H,s), 5.15-5.25(1H,m), 6.02(1H,brs), 6.47(1H,brd,J=7.3Hz), 6.86(1H,brd,J=7.3Hz), 7.0-7.2(2H,m), 7.3-7.5(5H,m)								
Reaction 2								
Compound I-a7:g	Pd(OH) <sub>2</sub> g	EtOH ml	Reaction time hr	Column sol.	Product	Amount g		
6.4	1.2	130	1.5	Not purified	I-b7	4.37		
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.63(3H,d,J=6.6Hz), 0.83(3H,d,J=6.6Hz), 1.03(3H,t,J=6.9z), 1.37(9H,s), 1.85-2.05(1H,m), 2.4-2.6(2H,m), 2.86(1H,d,J=4.0Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.55(1H,brs), 6.22(1H,brs), 6.4-6.6(1H,m), 6.64(1H,d,J=7.3Hz), 6.92(1H,brd,J=7.3Hz), 7.05(1H,brs), 7.90(1H,brd,J=8.3Hz)								

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Table D-22

Example 45(Continued from Table D-21)

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

Synthesis of 1-c18

Reaction 3								
Compound I-b7:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.17	1.06	1.7	4	13	EA:H 1:2	I-c18	0.56

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.3-0.9(9H,m), 1.2-1.5(18H,m), 2.2-2.4(1H,m), 2.6-3.4(6H,m), 3.9-4.1, 4.4-4.8, and 4.8-4.9(3H,m), 5.53(1H,brs), 6.25(1H,brs), 6.25-6.45(2H,m), 6.56(1H,brs), 6.6-6.9(1H,m), 6.9-7.1(3H,m), 7.15-7.3(2H,m), 7.6-7.8(1H,m)

Reaction 4a						
Compound I-c18 g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.51	2	4	1	MC:M 20:1	0.36	19.9

EI-MS(M<sup>+</sup>):528

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.60(3H,d,J=6.6Hz), 0.8-0.9(6H,m), 1.38(9H,s), 2.2-2.4(1H,m), 2.68(1H,dd,J=7.3,13.5Hz), 2.8-3.0(2H,m), 3.0-3.25(3H,m), 3.71(1H,t,J=6.9Hz), 4.21(1H,brd,J=10.9Hz), 4.4-4.6(1H,m), 5.55(1H,brs), 6.23(1H,brs), 6.64(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.7,7.9Hz), 6.9-7.0(1H,m), 6.97(2H,t,J=8.6Hz), 7.0-7.2(3H,m)

Table D-23

## Example 46

Synthesis of N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Me		Et		H		H		
Reaction 3								
Compound I-b7:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.0	1.23	1.06	1.7	4	14	MC:M 50:1	I-c 19	0.54
Reaction 4a								
Compound I-c19:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr		Column sol.	Amount g	HPLC min	
0.48	2	4	0.5		MC:M 20:1	0.26	20.4	
EI-MS(M <sup>+</sup> ):542								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.57, 0.68, 0.71, and 0.91(6H,d,J=6.6Hz), 0.99 and 1.05(3H,t,J=6.9Hz), 1.37(9H,s), 2.29 and 2.38(3H,s), 2.3-2.5(1H,m), 2.8-3.4(6H,m), 3.52 and 3.60(1H,t,J=6.6Hz), 3.6-3.9(1H,m), 4.5-4.7(1H,m), 5.66, 5.74, 5.83, and 6.25(2H,brs), 6.66-6.72(7H,m), 7.61(1H,brd,J=5.4Hz), 9.16(1H,d,J=7.6Hz)								

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Table D-24

## Example 47

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Et		Et		H		H	
Reaction 3							
Compound I-b7:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1	1.42	1.06	1.7	4	14	MC:M 50:1	I-c 20 0.86
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.35-1.2(12H,m), 1.36, 1.38, and 1.40(9H,s), 2.2-2.4(1H,m), 2.7-3.0 and 3.2-3.6(8H,m), 3.7-3.9, 4.1-4.3, 4.4-4.6, and 4.9-5.1(3H,m), 5.1-5.5(3H,m), 6.5-6.7, 6.8-7.0, and 7.0-7.4(12H,m), 7.6-7.8(1H,m).							
Reaction 4a							
Compound I-c20 g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.8	0.16	10	1	MC:M 20:1	0.31	20.6	
EI-MS(M <sup>+</sup> ):556							
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.45, 0.63, 0.67, and 0.73(6H,d,J=6.6Hz), 0.8-1.2(6H,m), 1.38(9H,s), 2.1-2.7(3H,m), 2.7-3.3(6H,m), 3.5-3.9(2H,m), 4.4-4.7(1H,m), 5.38(1H,brs), 5.4-5.6(1H,m), 5.9-6.3(1H,m), 6.62(1H,d,J=7.9Hz), 6.7-7.0(3H,m), 7.0-7.2(3H,m), 7.45-7.65(1H,m)							

Table D-25

## Example 48

## Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Et		H		Me		
Reaction 1								
Compound T2:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.95	6.62	6.57	8.3	120	2	EA:H 3:2	I-a8	9.0
Reaction 2								
Compound I-a8:g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
8.9	0.90	200	1.5		Not purified	I-b8	6.4	
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.64(3H,d,J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.05(3H,t,J=7.1Hz), 1.37(9H,s), 1.90-2.02(1H,m), 2.51(2H,q,J=6.9Hz), 2.73(3H,d,J=4.9Hz), 2.86(1H,d,J=4.3Hz), 2.91-3.07(2H,m), 4.53(1H,dd,J=7.2,15.2Hz), 6.04(1H,brd,J=4.6Hz), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.03(1H,d,J=2.0Hz), 7.88(1H,d,J=8.3Hz)								



Example 48(Continued from Table D-25)

### Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

Parameter	Value	Unit
Temperature	25	°C
Humidity	50	%
Light intensity	100	μmol/m <sup>2</sup> /s
CO <sub>2</sub> concentration	400	ppm
Water potential	-0.1	MPa
Soil moisture	0.6	g/g
Root length	10	cm
Stem diameter	2	cm
Leaf area	15	cm <sup>2</sup>
Chlorophyll content	25	mg/g
Protein content	10	mg/g
Starch content	5	mg/g
Cellulose content	2	mg/g
Lignin content	1	mg/g
Phenolic content	0.5	mg/g
Flavonoid content	0.2	mg/g
Carotenoid content	0.1	mg/g
Vitamin C content	0.05	mg/g
Vitamin E content	0.02	mg/g
Mineral content	0.01	mg/g
Trace element content	0.001	mg/g
Heavy metal content	0.0001	mg/g
Radioactive content	0.00001	mg/g
Biological activity	1	unit
Enzyme activity	1	unit
Antioxidant activity	1	unit
Antibacterial activity	1	unit
Antifungal activity	1	unit
Antiviral activity	1	unit
Anticancer activity	1	unit
Antidiabetic activity	1	unit
Antihypertensive activity	1	unit
Anticholesterol activity	1	unit
Antithrombotic activity	1	unit
Anticoagulant activity	1	unit
Antiparasitic activity	1	unit
Anticancer activity	1	unit
Antidiabetic activity	1	unit
Antihypertensive activity	1	unit
Anticholesterol activity	1	unit
Antithrombotic activity	1	unit
Anticoagulant activity	1	unit
Antiparasitic activity	1	unit



Table D-28

## Example 50

## Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Et		Et		H		Me		
Reaction 3								
Compound I-b8:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.52	1.53	1.13	1.23	20	96	EA:H 1:1	I-c23	520
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.41, 0.57, 0.62 and 0.72(total 6H,d,J=6.3-6.9Hz), 0.80-1.20(total 6H,m), 1.35, 1.38 and 1.40(total 9H,s), 2.22-2.42(1H,m), 2.66(3H,d,J=4.3Hz), 2.74-3.56(8H,m), 4.37(1H,dd,J=7.3,7.9Hz), 5.00-5.48(4H,m), 5.78-6.00(1H,m), 6.50-6.66(1H,m), 6.84-7.44(11H,m)								
Reaction 4b								
Compound I-c23:mg	Pd(OH) <sub>2</sub> mg	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min		
450	45	8	14	MC:M:N 20:1:1	308	21.6		
EI-MS(M <sup>+</sup> ):570								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.47, 0.64, 0.70 and 0.76(total 6H,d,J=6.3-6.6Hz), 0.88-1.24(6H,m), 1.38(9H,s), 2.10-2.64(3H,m), 2.70 and 2.71(total 3H,d,J=4.6Hz), 2.80-3.30(6H,m), 3.58-3.94(2H,m), 4.46(1H,dd,J=7.6-7.9Hz), 5.74-6.08(2H,m), 6.61(1H,d,J=7.9Hz), 6.78-7.20(6H,m), 7.38(1/2H,d,J=6.3Hz), 8.74(1/2H,d,J=7.9Hz)								

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Table D-29

## Example 51

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

SYNTHESIS OF 1,4-DIHYDRO-2,6-DIMETHYL-4-OXO-2-PYRIDINE CARBOXYLIC ACID

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Et		Me		H		
Reaction 1								
Compound T4:g	Compound V2 :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.360	4.500	4.113	3.73	110	20	H:ACT 3:2	I-a9	5.970
Reaction 2								
Compound I-a9:g	Pd-C g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
5.870	1.000	114	1		Not purified	I-b9	3.600	
Reaction 3								
CompoundI I-b9:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.200	1.350	1.220	1.33	6	18	H:EA 2:1	I-c24	1.160
Reaction 4a								
Compound I-c24:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr		Column sol.	Amount g	HPLC min	
1.06	5.00	10	1.5		MC:M: H 15:1:2	0.251	19.3	
EI-MS(M <sup>+</sup> ):542								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.30, 0.69, 0.82 and 0.85(6H,d, J=6.4-6.9 Hz), 0.92 and 1.12(3H,t,J=3.4-4.1Hz), 1.35 and 1.37(9H,s), 2.25-2.40(1H,m), 2.56-3.37(5H,m), 2.82 and 3.02(3H,s), 3.60-3.77(2H,m), 4.83-5.38(2H,m), 6.02band 6.18(2H,brs), 6.43 and 6.62(1H,d,J=6.8Hz), 6.82-7.15(6H,m)								

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Table D-30

## Example 52

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Me		Et		Me		H	
Reaction 3							
CompoundI I-b9:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product  Amount g
1.200	1.420	1.220	1.33	7	30	H:EA 1:2	I-c25  0.740
Reaction 4a							
Compound I-c25:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.674	3.00	10	2	MC:M:H 10:1:2	0.278	20.0	
EI-MS(M <sup>+</sup> ):556							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.42, 0.78, 0.84 and 0.91(6H,d, J=6.3-6.9 Hz), 0.94 and 1.18(3H, t, J=3.6Hz), 1.35 and 1.37(9H, s), 2.20-2.34(1H,m), 2.29(3H,s), 2.62-3.02(4H,m), 2.93 and 3.04(3H,s), 3.17-3.31(2H,m), 3.45-3.72(1H,m), 5.02 and 5.22(1H, d,J=10.7-10.9 Hz), 5.09 and 5.17(1H,t,J=5.8-6.1Hz), 5.69, 6.07 and 6.57(2H,brs), 6.45 and 6.64(1H,d,J=8.0Hz), 6.78-7.14(6H,m)							

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Table D-31

## Example 53

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Et		Et		Me		H		
Reaction 3								
Compound I	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
I-b9:g								
1.020	1.640	1.220	1.33	8	12	MC:M:H 20:1:1	I-c26	1.040

Reaction 4b						
Compound I-c26:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.934	0.093	20	3	MC:M:H =15:1:2	0.201 0.103	20.7 22.4

Compound of which yeilded amount was 0.201 g with HPLC retention time of 20.7 min.

EI-MS(M<sup>+</sup>):570

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): (two rotamers) δ 0.42,0.79,0.84 and 0.91(6H,d and m, J=6.3-6.9Hz), 1.02 and 1.11(6H,t,J=3.6Hz), 1.33 and 1.40(3H,s), 2.20-3.36(9H,m), 2.92 and 3.03(3H,s), 3.51-3.75(1H,m), 5.00-5.38(2H,m), 6.02 and 6.58(2H,brs), 6.42-6..62(1H, d, J=8.0Hz), 6.82-7.20(6H, m)

Compound of which yeilded amount was 0.103 g with HPLC retention time of 22.4 min.

EI-MS(M<sup>+</sup>):570

<sup>1</sup>H-NMR (CDCl<sub>3</sub>): (two rotamers) δ 0.13 and 0.79(4H, t, J=3.4 Hz), 0.62 and 0.89(2H, d, J=6.3-6.9Hz), 0.97 and 1.05(6H,t,J=3.6Hz), 1.34 and 1.41(9H,s), 1.92-2.03(1H,m), 2.21-2.60(2H, m), 3.00 and 3.08(3H,s), 2.74-3.25(4H,m), 3.60-3.72(1H,m), 4.62(1H,d,J=8.0Hz), 4.78-4.82(1H,m), 5.18-5.36(2H,m), 6.02(1H,brs), 6.59 and 6.63(1H,d,J=8.0Hz), 6.81-6.98(3H,m), 7.09-7.20(3H,m)

Table D-32

## Example 54

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

SYNTHESIS OF 1a

R <sub>31</sub>	R <sub>32</sub>	R <sub>33</sub>	R <sub>34</sub>
H	Et	Me	Me

Reaction 1								
Compound T5:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.93	5.0	4.56	5.0	150	12	EA:H 2:1	I-a10	5.02

EI-MS(M<sup>+</sup>):525

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.23-1.08(9H,m), 1.34, 1.37, 1.39(9H,s), 2.10-3.56(10H,m), 4.25-5.33(5H,m), 6.00-7.48(9H,m)

Reaction 2						
Compound I-a10:g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time min	Column sol.	Product	Amount g
4.92	0.50	94	40	CH:M:N 100:10:1	I-b10	3.42

<sup>1</sup>H-NMR(CDCl<sub>3</sub>):δ 0.35, 0.69, 0.88, 0.95(6H,d,J=6.6-6.9Hz), 0.82, 1.03(3H,t,J=7.1Hz), 1.37(9H,s), 1.66-1.83(1H,m), 1.92(2H,dd,J=13.9,6.6Hz), 2.76,2.79(3H,d,J=4.8Hz), 2.89, 2.99(3H,s), 2.92-3.23(2H,m), 4.55, 5.46(1H,dd,J=10.9,4.0Hz), 5.71, 5.89(1H,brs), 6.13, 8.19(1H,m), 6.55, 6.60(1H,d,J=7.9Hz), 6.78, 6.91(1H,dd,J=7.9,1.7Hz), 7.00, 7.07(1H,d,J=1.7Hz)

Table D-33

Example 54(Continued from Table D-32)

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

Reaction 3										
Compound I-b10:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg		
1.15	1.25	1.13	1.23	20	13	EA:H 2:1	I-c27	434		
Reaction 4a										
Compound I-c27:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min				
434	2	2	2.5	EA:EtOH =10:1	86.0 26.8	20.6 22.8				
Compound of which yeilded amount was 86.0 mg with HPLC retention time of 20.6 min. EI-MS(M <sup>+</sup> ):556 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.27-1.18(9H,m), 1.35,1.39(9H,s), 2.15-3.77(12H,m), 2.84, 3.06(3H,s), 4.87-5.27(2H,m), 5.99-7.20(8H,m)										
Compound of which yeilded amount was 26.8 mg with HPLC retention time of 22.8 min. EI-MS(M <sup>+</sup> ):556 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.16, 0.40, 0.55, 0.84(6H,d,J=6.3-6.9Hz), 0.83, 1.01(3H,t,J=7.1Hz), 1.36,1.41(9H,s), 2.00-2.21(1H,m), 2.67,2.76(3H,d,J=4.8Hz), 3.05,3.09(3H,s), 2.81-3.30(7H,m), 3.68-3.87(1H,m), 3.72, 3.80(1H,dd,J=7.8,6.1Hz), 4.61, 5.10(1H,d,J=10.7Hz), 4.66, 5.24(1H,dd,J=9.7,6.4Hz), 6.05-7.20(8H,m)										

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Table D-34

## Example 55

## Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Me		Et		Me		Me		
Reaction 3								
Compound I-b10:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.0	1.14	0.98	1.07	17	14	EA:H 2:1	I-c28	322
Reaction 4a								
Compound I-c28:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
322	2	2	2	EA:EtOH 10:1	101 38	21.1 22.6		
Compound of which yeilded amount was 101 mg with HPLC retention time of 21.1 min.								
EI-MS(M <sup>+</sup> ):570								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.41, 0.79, 0.86, 0.90(6H,d,J=6.3-6.9Hz), 0.94, 1.15(3H,t,J=7.3Hz), 1.34, 1.39(9H,s), 2.27, 2.28(3H,s), 2.71, 2.76(3H,d,J=4.8Hz), 2.15-3.78(9H,m), 2.93,3.08(3H,s), 4.98-5.32(2H,m), 6.03-7.20(8H,m)								
Compound of which yeilded amount was 38 mg with HPLC retention time of 22.6 min.								
EI-MS(M <sup>+</sup> ):570								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): δ 0.10, 0.14, 0.63, 0.85(6H,d,J=6.3-6.9Hz), 0.82, 0.95(3H,t,J=7.1Hz), 1.35, 1.40(9H,s), 2.18, 2.54(3H,s), 2.71, 2.75(3H,d,J=4.8Hz), 2.99, 3.08(3H,s), 1.89-3.27(8H,m), 3.46-3.64(1H,m), 4.54, 5.19(1H,d,J=10.6Hz), 4.66, 5.23(1H,t,J=7.3Hz), 6.51, 6.60(1H,d,J=7.9Hz), 6.07-7.20(7H,m)								

TOTAL 67206960

### Example 56

### Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

[illegible]

Table D-36

## Example 57

Synthesis of Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
H		Et		Et		H	
Reaction 1							
Compound d T7:g	Compound d V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
16.000	24.088	23.200	25.32	400.00	60	EA:H:MC 3:2:2	I-a11 16.000
Reaction 2							
Compound I-a11:g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr	Column sol.	Product Amount g		
9.000	0.900	200.00	2	MC:M:H 15:1:2	I-b11 4.000		
Reaction 3							
Compound I-b11:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.100	1.150	1.040	1.13	10.00	72	EA:H:MC 3:2:2	I-c30 0.700
Reaction 4a							
Compound I-c30:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.650	2.00	2.00	2	MC:M:H 15:1:2	0.180	20.9	
EI-MS(M <sup>+</sup> ):542							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.51, 0.82, 0.87 and 0.94(6H,d,J=6.6~6.9Hz), 0.82~1.31(6H,m), 1.35 and 3.81(9H,s), 2.21~3.82 (9H,m) 4.83~5.30(3H,m), 6.62 and 6.54(1H,d,J=7.9Hz), 6.80~7.21(6H,m)							

Table D-37

## Example 58

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Me		Et		Et		H	
Reaction 3							
Compound I-b11:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.240	1.360	1.170	1.28	10.00	72	EA:H:MC 3:2:2	I-c31 0.300
Reaction 4a							
Compound I-c31:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.280	2.00	2.00	2	MC:M:H 15:1:2	0.170	21.2	
EI-MS(M <sup>+</sup> ):570							
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.63~1.30(9H, m and d, J=6.3Hz),, 1.34 and 1.39(9H, s), 2.30(3H,s), 2.22~3.90(9H,m), 4.97~5.33(3H,m), 6.43 and 6.62(1H,d,J=7.92), 6.81~7.19(6H, m)							

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Table D-38

## Example 59

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

SYNTHESIS OF 1,3,5-TRISUBSTITUTED BENZENES

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
Et		Et		Et		H		
Reaction 3								
Compound I-b11:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.500	1.980	1.470	1.60	10.00	72	EA:H:MC 3:2:2	I-c32	0.700
Reaction 4b								
Compound I-c32:g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.650	0.065	10.00	2	MC:M:H 15:1:2	0.240	20.0		
EI-MS(M <sup>+</sup> ):458								
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.85~1.27(15H, m), 1.37 and 1.39(9H, s), 2.03~3.63(11H, m), 4.50~4.55(1H, m), 5.02~5.34(2H, m), 6.43 and 6.60(1H, d, J=8.24), 6.81~7.19(6H, m)								

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Table D-41

## Example 62

## Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>	
Et		Et		Et		Me	
Reaction 3							
Compound I I-b12:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.000	1.277	0.945	1.10	6.00	48	MC:M:H 20:1:1	I-c35 0.540
Reaction 4b							
Compound I-c35:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.501	0.050	67	2	MC:M:H 25:1:3	0.240	23.2	
EI-MS(M <sup>+</sup> ):598 <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) $\delta$ 0.64 and 0.84-0.92(6H, d and m, J=7.9Hz), 1.04, 1.05 and 1.13(6H,t,J=6.3Hz), 1.33 and 1.39(3H, s), 2.21-2.94(6H,m), 3.12-3.80(6H,m), 4.82-5.08(1H, m), 5.13 and 5.20(1H,d,J=9.7Hz), 6.47 and 6.58(1H,d,J=8.8Hz), 6.79-7.19(6H,m)							

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Table D-42

## Example 63

## Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu

synthesis of Phe(4-1), N-Ne

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>		
H		Me		H		tBu		
Reaction 1								
Compound T18:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.58	0.55	0.56	0.61	10	2	EA:H 1:3	I-a13	1.0
Reaction 2								
Compound I-a13:g	Pd(OH) <sub>2</sub> g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
1.0	0.16	20	5		Not purified	I-b13	0.75	
Reaction 3								
Compound I-b13:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.37	0.34	0.33	0.38	4	14	MC:M:N 50:1:0. 1	I-c36	0.58
Reaction 4a								
Compound I-c36:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time min		Column sol.	Amount g	HPLC min	
0.49	2	4	30		MC:M:N 30:1:0.1	0.31	23.4	
EI-MS(M <sup>+</sup> ):570								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.72(2H,d,J=6.9Hz), 0.82(1H,d,J=6.6Hz), 0.92-0.96(3H,m), 1.19(3H,s), 1.22(6H,s), 1.37(3H,s), 1.38(6H,s), 2.2-2.4(1H,m), 2.5-3.0(32/5H,m), 3.17(3/5H,dd,J=4.9,13.9Hz), 3.61(3/5H,br), 3.82(2/5H,br), 3.96(3/5H,d,J=10.9Hz), 4.3-4.6(7/5H,m), 5.25(1/3H,s), 5.41(1/3H,br), 5.48(2/3H,s), 6.03(2/3H,br), 6.6-6.8(2H,m), 6.9-7.2(5H,m), 9.00(1H,d,J=7.9Hz)								

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Table D-43

## Example 64

Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>SO<sub>2</sub>CH<sub>3</sub>

R <sub>31</sub>		R <sub>32</sub>		R <sub>33</sub>		R <sub>34</sub>				
H		Me		Me		CH <sub>2</sub> SO <sub>2</sub> CH <sub>3</sub>				
Reaction 1										
Compound T17:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g		
0.840	0.782	0.753	0.8 2	10	15	EA:H:MC 3:2:2	I-a14	1.200		
Reaction 2										
Compound I-a14:g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g			
1.100	0.150	30.00	2		Not purified	I-b14	0.850			
Reaction 3										
CompoundI I-b14:g	Compound :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g		
0.850	0.710	0.572	0.62	10.00	17	EA:H:MC 1:1:1	I-c37	1.020		
Reaction 4a										
Compound I-c37:g	Pd(OH) <sub>2</sub> :g	MeOH ml	Reaction time hr		Column sol.	Amount g	HPLC min			
1.020	0.150	30.00	2		MC:M:H 15:1:2	0.530	20.2			
EI-MS(M <sup>+</sup> ):620										
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): (two rotamers) δ 0.78(3H, dd, J=6.6, 12.1Hz), 0.91(3H, dd, J=6.6, 11.2Hz), 1.26 and 1.35(9H, s), 2.00(3H,s), 2.55, 2.63, 2.75, 2.84, 2.99 and 3.16(8H,s), 2.21 ~ 5.30(11H, m), 6.43 and 6.55(1H, d, J=7.9Hz), 6.76~7.13(6H, m)										

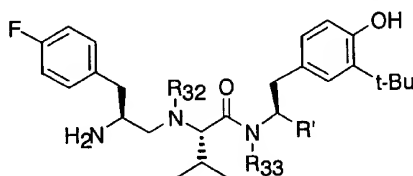
- 5 Examples of compounds synthesized according to the scheme 2 are shown in Tables D-44 to D-66.

Table D-44

## Example 65

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoyl-ethyl)-N-methyl-3-methylbutanamide

Structural Formula of Compounds of Example 65-78



R <sub>32</sub>		R <sub>33</sub>		R'				
H		Me		CONH <sub>2</sub>				
Reaction 1								
Compound T4:g	Compound V4:g	CMPI :g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
5.78	6.97	7.08	8.05	115	19	EA:H 1:1	I-d1	9.50
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.63, 0.74, 0.89 and 0.94(total 6H,d,J=6.6-6.9Hz), 1.36 and 1.39(total 9H,s), 1.90-2.04(1H,m), 2.80-3.38(2H,m), 2.96 and 3.04(total 3H,s), 4.14-4.22(1/2H,m), 4.40-4.50(1/2H,m), 4.60-4.70(1/2H,m), 4.88-5.40(11/2H,m), 5.88(1/2H,brs), 6.49(1/2H,d,J=7.9Hz), 6.58(1/2H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 7.02-7.14(1H,m), 7.30-7.40(5H,m)								
Reaction 2								Crude Compound I-e1 was used in Reaction 3.
Compound I-d1:g	Pd-C g	MeOH ml	Reaction time hr					
4.23	0.50	100	2					

Table D-45

Example 65(Continued from Table D-44)

Synthesis of 2-(2-amino-3-(4-

- 5 fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoyl-ethyl)-N-methyl-3-methylbutanamide

Reaction 3								
Compound I-el	Compound d P5:g	NaBH <sub>3</sub> C N g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
Crude compound of Reaction 2	2.37	1.16	1.01	90	1	EA:H 1:1	I-f1	2.08
EI-MS(M <sup>+</sup> ):600 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.86 and 1.02(total 6H,d,J=6.6-6.9Hz), 1.31, 1.35, 1.37 and 1.43(total 18H,s), 1.56-1.80(3H,m), 2.58-3.20(7H,m), 3.56-3.66(1H,m), 4.51(1H,d,J=8.6Hz), 5.28(1H,brs), 5.58-5.68(1H,m), 5.93(1H,brs), 6.53(1H,d,J=8.2Hz), 6.82-7.22(7H,m)								
Reaction 7								
Compound I-f1:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
360	3	3	0.5	MC:M:N 10:1:0.1	275	17.8		
EI-MS(M <sup>+</sup> ):500 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.47, 0.67, 0.92 and 0.95(total 6H,d,J=6.3-6.6Hz), 1.38(9H,s), 1.64-1.80(2H,m), 1.97(1H,dd,J=5.3,11.6Hz), 2.28(1H,dd,J=9.2,13.5Hz), 2.72(1H,dd,J=4.0,13.5Hz), 2.80-3.02(3H,m), 2.94(3H,s), 3.18(1H,dd,J=5.8,14.5Hz), 5.31(1H,brs), 5.55(1H,dd,J=5.9,10.9Hz), 6.00(1H,brs), 6.59(1H,d,J=8.2Hz), 6.89(1H,dd,J=1.9,8.2Hz), 6.97(2H,t,J=8.2Hz), 7.11(2H,t,J=8.2Hz), 7.11(1H,d,J=1.9Hz)								

Table D-46

## Example 66

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-

- 5 methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
Me		Me		CONH <sub>2</sub>				
Reaction 4								
Compound I-fl:mg	HCHO ml	NaBH <sub>3</sub> CN mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
530	0.38	117	0.10	8	0.5	H:A 1:1	I-gl	532
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.76, 0.78 and 0.94 (total 6H, d, J=5.2-6.6Hz), 1.37 and 1.38 (total 18H, s), 1.58-1.76 (4H, m), 1.94-2.30 (2H, m), 2.49 and 2.89 (total 3H, s), 2.60-3.22 (4H, m), 3.58-3.76 (1H, m), 4.38 and 4.62 (total 1H, d, J=8.6Hz), 5.22-5.30 (1H, m), 5.64-5.72 (1H, m), 6.07 (1H, brs), 6.52-6.62 (1H, m), 6.94-7.12 (6H, m)								
Reaction 7								
Compound I-gl:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
465	4	4	1	CH:M:N 10:1:0.1	280	21.5		
FAB-MS: 515 (M+H <sup>+</sup> )								
<sup>1</sup> H-NMR(CD <sub>3</sub> OD):δ 0.14, 0.83, 0.89 and 1.01 (total 6H, d, J=6.3-6.6Hz), 1.40 and 1.43 (total 9H, s), 1.84-2.18 (2H, m), 2.10 (3H, s), 2.38-2.50 (1H, m), 2.60-3.04 (3H, m), 2.91 and 3.06 (total 3H, s), 3.18-3.30 and 3.58-3.66 (total 3H, m), 4.70 and 5.61 (total 1H, dd, J=4.3-5.0, 10.9Hz), 6.66 and 6.69 (total 1H, d, J=7.9Hz), 6.92 and 6.96 (total 1H, dd, J=1.3, 7.9Hz), 7.04-7.34 (5H, m)								

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Table D-47

## Example 67

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'			
Ac		Me		CONH <sub>2</sub>			
Reaction 5							
Compound I-fl:mg	Ac <sub>2</sub> O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
451	3	42.9	5	15	EA:H 1:1	I-h1	306
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.13, 0.60 and 0.87(total 6H,d,J=6.3-6.6Hz), 1.23, 1.26, 1.32 and 1.36(total 18H,s), 2.06-2.30(3H,m), 2.15, 2.16 and 2.31(total 6H,s), 2.48(1H,dd,J=7.9,13.2Hz), 2.74-2.94(2H,m), 3.05 and 3.07(total 3H,s), 3.28-3.42(2H,m), 3.88-4.00(1H,m), 4.88(1H,d,J=8.6Hz), 5.08-5.42(3H,m), 6.31(1H,brs), 6.92(2H,d,J=8.2Hz), 6.98(2H,d,J=8.2Hz), 7.08-7.26(3H,m)							
Reaction 6							
Compound I-h1:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg	
412	1	4	1	EA:H 1:1	I-i1	341	
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.05, 0.11, 0.52 and 0.61(total 6H,d,J=6.3-6.9Hz), 1.36, 1.37 and 1.42(total 18H,s), 1.70 and 2.05(total 3H,s), 2.00-2.42(2H,m), 2.80-3.40(5H,m), 3.04 and 3.07(total 3H,s), 3.64-3.88(1H,m), 4.76-5.32(5H,m), 5.92(1H,brs), 6.56(1H,d,J=8.2Hz), 6.88-7.30(6H,m)							

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Table D-48

Example 67(Continued from Table D-47)

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

Reaction 7						
Compound I-11 mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min
330	3	2	0.5	CH:M 10:1	210	23.4
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.31, 0.69, 0.81 and 0.86 (total 6H, d, J=6.3-7.0Hz), 1.38(9H, s), 1.78-1.86(1H, m), 1.85(3H, s), 2.5-2.94(3H, m), 3.05 and 3.07 (total 3H, s), 3.04-3.30(1H, m), 3.50-3.84(2H, m), 4.10 and 4.40 (total 1H, brs), 4.63 and 4.66 (total 1H, brs), 5.06(1H, d, J=10.2Hz), 5.16-5.32(2H, m), 6.54 and 6.65 (total 1H, d, J=7.9-8.2Hz), 6.80 and 6.93 (total 1H, dd, J=1.5-2.0, 7.9-8.2Hz), 6.98-7.14(5H, m)						

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Table D-49

## Example 68

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>			R'			
H		Et			CONH <sub>2</sub>			
Reaction 1								
Compound T7:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.01	1.25	1.27	1.23	10	19	EA:H 1:1	I-d2	0.75
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.72,0.87, 0.92 and 0.95(total 6H,d,J=6.6-6.9Hz), 1.14-1.30(3H,m), 1.37 and 1.38(total 9H,s), 1.86-1.98(1H,m), 2.76(1/4H,dd,J=6.6,13.8Hz), 3.12(3/4H,dd,J=7.9,13.9Hz), 3.24-3.56(3H,m), 4.20 and 4.33(total 1H,dd,J=6.6-8.6,8.9Hz), 4.60 and 4.71(total 1H,t,J=7.2-7.6Hz), 5.02-5.28(7/2H,m), 5.36(1H,d,J=8.6Hz), 6.26(1/2H,brs), 6.54 and 6.58(total 1H,d,J=7.9-8.2Hz), 6.84-6.92(total 1H,m), 7.08(1H,d,J=1.7Hz), 7.20-7.40(5H,m)								
Reaction 2								
Compound I-d2:g	Pd-C g	MeOH ml	Reaction time hr		Crude Compound I-e2 was used in Reaction 3.			
0.62	0.10	12	1					



Table D-50

Example 68(Continued from Table D-49)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

Reaction 3								
Compound I-e2	Compound d P5:mg	NaBH <sub>3</sub> CN mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
Crude compound of Reaction 2	400	124	0.4	10	1	EA:H 1:1	I-f2	298
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.65, 0.87, 0.90 and 1.02(total 6H,d,J=6.2-6.9Hz), 1.12 and 1.24(total 3H,t,J=6.9-7.3Hz), 1.35, 1.37, 1.38 and 1.41(total 18H,s), 1.50-1.82(3H,m), 2.58-3.64(7H,m), 4.28-4.54(1H,m), 5.04-5.36(2H,m), 6.20-6.32 and 6.52-6.64(2H,m), 6.80-7.12(6H,m)								
Reaction 7								
Compound I-f2 mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
331	2	3	0.5	MC:M 20:1	234	19.7		
EI-MS(M <sup>+</sup> ):514								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.56, 0.75, 0.94 and 0.96(total 6H,d,J=6.6-6.9Hz), 1.17 and 1.26(total 3H,t,J=6.9-7.3Hz), 1.38(9H,s), 1.50-1.80(2H,m), 1.98(1H,dd,J=8.6,11.2Hz), 2.20-2.50(2H,m), 2.71(1H,dd,J=3.8,13.2Hz), 2.88-3.50(5H,m), 4.54-4.62 and 4.94-5.02(1H,m), 5.21 and 6.40(total 1H,brs), 6.58(1H,d,J=8.2Hz), 6.82-7.18(6H,m)								

Table D-51

## Example 69

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
H		H		CH <sub>2</sub> OH				
Reaction 1								
Compound T19:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.2	1.62	1.65	1.8	50	1.5	EA:H 1:1	I-d3	2.2
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.81(3H,brd,J=6.3Hz), 0.91(3H,d,J=6.6Hz), 1.38(9H,s), 2.0-2.2(1H,m), 2.49(1H,brs), 2.6-2.9(2H,m), 3.5-3.7(2H,m), 3.92(1H,dd,J=5.,7.9Hz), 5.11(2H,s), 5.1-5.3(2H,m), 6.09(1H,brd,J=7.6Hz), 6.57(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.3,7.9Hz), 7.04(1H,d,J=1.3Hz), 7.36(5H,s)								
Reaction 2								
Compound I-d3 g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.2	0.2	48	12	Not purified	I-e3	1.6		
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.57(3H,d,J=6.6Hz), 0.89(3H,d,J=6.9Hz), 1.38(9H,s), 2.1-2.3(1H,m), 2.68(1H,dd,J=8.9,13.9Hz), 2.86(1H,dd,J=6.3,13.9Hz), 3.23(1H,d,J=3.6Hz), 3.62(1H,dd,J=6.3,10.9Hz), 3.75(1H,dd,J=3.6,10.9Hz), 4.0-4.2(1H,m), 5.45(1H,brs), 6.61(1H,d,J=7.9Hz), 6.90(1H,dd,J=2.0,7.9Hz), 7.05(1H,d,J=2.0Hz), 7.56(1H,brd,J=6.6Hz)								

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Table D-52

Example 69(Continued from Table D-51)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

Reaction 3								
Compound I-e3:g	Compound P5:g	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.8	0.8	0.33	0.28	25	1.5	CH:M:N 300:10:1	I-f3	1.05
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.69(3H,brd,J=5.9Hz), 0.81(3H,d,J=6.9Hz), 1.38(9H,s), 1.42(9H,s), 1.8-2.0(1H,m), 2.35-3.0(6H,m), 3.0-3.2(1H,m), 3.5-3.9(3H,m), 4.1-4.3(1H,m), 4.5-4.7(1H,m), 5.47(1H,brs), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.36(1H,brd,J=7.6Hz)								

Reaction 7						
Compound I-f3:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.3	0.5	5	10	CH:M:N 200:10:1	0.21	17.7
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):0.72(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.8-2.0(1H,m), 2.4-2.9(7H,m), 2.9-3.1(1H,m), 3.50(1H,dd,J=4.6,11.6Hz), 3.66(1H,dd,J=3.0,11.6Hz), 4.1-4.3(1H,m), 6.60(1H,d,J=7.9Hz), 6.92(1H,dd,J=1.7,7.9Hz), 7.0-7.2(6H,m), 7.35(1H,brd,J=8.3Hz)						

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Table D-53

## Example 70

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

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R <sub>32</sub>		R <sub>33</sub>		R'				
Me		H		CH <sub>2</sub> OH				
Reaction 4								
Compound I-f3:g	HCHO ml	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.34	0.23	0.077	0.07	6	1.5	CH:M:N 300:10:1	I-g3	0.33
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.82(3H,d,J=6.3Hz), 0.94(3H,d,J=6.6Hz), 1.37(9H,s), 1.41(9H,s), 2.06(3H,s), 2.1-2.6(4H,m), 2.70(1H,dd,J=8.9,14.2Hz), 2.8-3.0(2H,m), 3.5-3.8(3H,m), 4.2-4.5(2H,m), 5.62(1H,brs), 6.4-6.6(1H,m), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m)								
Reaction 7								
Compound I-g3:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.3	0.5	5	10	CH:M:N 200:10:1	0.17	20.1		
EI-MS(M <sup>+</sup> ):487								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):0.79(3H,d,J=6.6Hz), 0.94(3H,d,J=6.6Hz), 1.39(9H,s), 1.9-2.2(1H,m), 2.22(3H,s), 2.2-2.4(3H,m), 2.51(1H,d,J=8.9Hz), 2.6-2.8(2H,m), 2.87(1H,dd,J=6.6,14.2Hz), 3.0-3.2(1H,m), 3.57(1H,dd,J=5.3,10.9Hz), 3.72(1H,dd,J=3.6,10.9Hz), 4.1-4.3(1H,m), 6.19(1H,brd,J=7.3Hz), 6.63(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 6.98(2H,t,J=8.6Hz), 7.0-7.2(3H,m)								

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Table D-54

## Example 71

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
H		Me		Me				
Reaction 1								
Compound T20:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.62	2.22	2.25	2.46	36	16	EA:H 1:1	I-d4	2.74
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): δ 0.67, 0.72, 0.89 and 0.95 (total 6H, d, J=6.6-6.9Hz), 1.08 and 1.20 (total 3H, d, J=6.6-6.9Hz), 1.37 and 1.39 (total 9H, s), 1.88-2.02 (1H, m), 2.60-2.90 (2H, m), 2.89 (3H, d, J=3.3Hz), 4.30-4.46 (1H, m), 4.90-5.00 (1H, m), 5.07 (2H, s), 6.48 and 6.59 (total 1H, d, J=7.9Hz), 6.78-6.88 (1H, m), 7.00-7.08 (1H, m), 7.30-7.40 (5H, m)								
Reaction 2								
Compound I-d4:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.68	0.25	50	18	MC:M 20:1	I-e4	1.35		
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ): δ 0.68, 0.85, 0.95 and 0.99 (total 6H, d, J=6.6-6.9Hz), 1.11 and 1.24 (total 3H, d, J=6.6Hz), 1.88-2.04 (1H, m), 2.58-2.70 (2H, m), 2.83 and 2.91 (total 3H, s), 3.56-3.64 (1H, m), 3.95 and 4.99 (total 1H, ddd, J=6.6, 6.9, 7.6Hz), 6.62 and 6.67 (total 1H, d, J=7.9Hz), 6.77 and 6.88 (total 1H, dd, J=1.7, 7.9Hz), 6.98 and 7.02 (total 1H, d, J=1.7Hz)								

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Table D-55

Example 71(Continued from Table D-54)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

Reaction 3												
Compound d I-e4:g	Compound d P5:g	NaBH <sub>3</sub> CN mg	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g				
1.26	1.58	521	0.45 3	40	1	EA:H 1:4	I-f4	1.52				
<sup>1</sup> H-NMR (CDCl <sub>3</sub> ):δ 0.74, 0.85 and 0.99(total 6H,d,J=6.6-6.9Hz), 1.16(3H,d,J=6.9Hz), 1.30, 1.41 and 1.44(total 18H,s), 1.50- 1.70(3H,m), 2.36-2.90(7H,m), 3.52-3.68(1H,m), 4.54-4.64(1H,m), 5.22-5.38(1H,m), 6.51 and 6.60(total 1H,d,J=7.9Hz), 6.80- 7.20(6H,m)												
Reaction 7												
Compound I-f4:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol		Amount mg	HPLC min					
330	2	3	0.5	CH:M:N 10:1:0.1		224	20.8					
EI-MS(M <sup>+</sup> ):471												
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.80, 0.91 and 0.92(total 6H,d,J=6.6Hz), 1.15(3H,d,J=6.9Hz), 1.38 and 1.41(total 9H,s), 1.64- 2.04(4H,m), 2.28-3.14(5H,m), 2.79 and 2.92(total 3H,s), 3.90- 4.02 and 5.10-5.24(total 1H,m), 6.62 and 6.65(total 1H,d,J=7.4-7.6Hz), 6.74-7.20(6H,m)												

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### Example 72

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-

5 methylethyl)-N-methyl-3-methylbutanamide

$R_{32}$	$R_{33}$	$R'$
Me	Me	Me

#### Reaction 4

Compound I -f4:g	HCHO ml	NaBH <sub>3</sub> CN mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
520	0.39	120	0.105	9	0.5	H:EA 2:1	I-g4	404

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.28, 0.74, 0.81 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.17 and 1.21(total 3H,d,J=6.6-6.9Hz), 1.37 and 1.39(total 18H,s), 1.50-1.60(1H,m), 1.58(3H,s), 1.80-2.52(4H,m), 2.60-3.14(3H,m), 2.71(3H,s), 3.62-3.78(1H,m), 4.42-4.54(1H,m), 5.32-5.44(1H,m), 6.50-7.12(8H,m)

### Reaction 7

Compound I-g4:mg	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column sol.	Amount mg	HPLC min
386	2	4	0.5	CH:M 10:1	272	24.5

FAB-MS: 486 (M+H<sup>+</sup>)

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.44, 0.79, 0.93 and 0.96 (total 6H, d, J=6.6-6.9Hz), 1.13 and 1.20 (total 3H, d, J=6.6-6.9Hz), 1.39 and 1.41 (total 9H, s), 1.50-1.98 (3H, m), 2.04-2.18 (1H, m), 2.13 and 2.30 (total 3H, s), 2.32-3.10 (5H, m), 2.80 and 2.86 (total 3H, s), 4.18-4.28 and 5.24-5.36 (total 1H, m), 6.57 and 6.61 (total 1H, d, J=7.9Hz), 6.72-7.18 (6H, m)

Table D-57

## Example 73

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

## 5 hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'			
Ac		Me		Me			
Reaction 5							
Compound I-f4:mg	Ac <sub>2</sub> O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
735	4	158	6	16.5	EA:H 1:2	I-h4	489
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.13, 0.54, 0.58 and 0.86(total 6H,d,J=6.3-6.6Hz), 1.13 and 1.15(total 3H,d,J=6.3Hz), 1.30, 1.33, 1.36 and 1.42(total 18H,s), 1.69, 2.08, 2.13 and 2.31(total 6H,s), 2.02-2.84(5H,m), 2.91 and 2.96(total 3H,s), 3.14-3.40(2H,m), 3.82-4.04(1H,m), 4.70-5.28(2H,m), 6.88-7.30(7H,m)							
Reaction 6							
Compound I-h4:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg	
470	1	6	1	Not purified	I-i4	440	
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.11, 0.12, 0.51 and 0.64(total 6H,d,J=5.9-6.6Hz), 1.09 and 1.13(total 3H,d,J=6.3-6.6Hz), 1.37, 1.38, 1.40 and 1.43(total 18H,s), 1.66 and 2.03(total 3H,s), 2.00-2.44(3H,m), 2.62-2.72(2H,m), 2.68 and 2.92(total 3H,s), 2.88-3.40(2H,m), 3.72-3.88(1H,m), 4.52-5.32(2H,m), 6.52-7.34(7H,m)							

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[illegible][illegible][illegible][illegible][illegible]

Table D-59

## Example 74

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
H		H		Me				
Reaction 1								
Compound T21:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
3.000	4.350	4.400	6.00	80	5	H:EA:MC 5:1:1	I-d5	4.000
Reaction 2								
Compound I-d5:g	Pd(OH) <sub>2</sub> : g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g		
4.000	0.400	100	1	MC:Me:H 10:1:1	I-e5	1.200 and 0.500 (diastereomers)		
Reaction 3								
Compound I-e5:g	Compound P5:g	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column . sol	Product	Amount g
1.200	1.100	0.490	0.30	30	2	H:EA:M C 3:2:2	I-f5	0.730
0.480	0.628	0.207	0.3	10	2	H:EA 1:1		0.620

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Table D-60

Example 74(Continued from Table D-59)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

Reaction 7						
Compound I-f5:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.500	2.00	2	1	MC:M:H 10:1:1	0.320	20.7
0.113	1.00	2	1	CH:M:N 300:10:1	0.063	20.4
Compound of which yielded amount was 0.320 g with HPLC retention time of 20.7 min. EI-MS(M <sup>+</sup> ):457 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.73(3H, d, J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.08(3H,d, J=6.3Hz), 1.37(9H,s), 1.81~2.00(1H,m), 2.28- 2.80(9H,m), 2.90-3.00(1H,m), 4.21~4.38 (1H,m), 6.68(1H,d,J=8.2Hz), 6.83~7.18(6H,m) Compound of which yielded amount was 0.063 g with HPLC retention time of 20.4 min. EI-MS(M <sup>+</sup> ):457 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.88 and 0.92(6H,d,J=6.9Hz), 1.14(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.10(1H,m), 2.18- 2.44(3H,m), 2.84-2.96(4H,m), 3.63-3.75(1H,m), 4.22- 4.31(1H,m), 6.60(1H,d,J=6.8Hz), 6.86-7.26(6H, m)						

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Table D-61

## Example 75

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-  
N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-  
5 methylethyl)-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'	
Me		H		Me	

Reaction 4								
Compound I I-f5:g	HCHO ml	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.400	0.32	0.093	0.30	10	2	H:EA:MC 3:1:1	I-g5	0.300
0.500	0.38 0	0.118	0.10	9	2	H:EA:MC 2:1:1		0.320

Reaction 7						
Compound I-g5:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.240	1.00	1	1	MC:M:H 10:1:1	0.140	23.0
0.320	2.00	4	1	CH:M:N 300:10:1	0.226	22.5

Compound of which yielded amount was 0.140 g with HPLC retention time of 23.0 min.  
EI-MS(M<sup>+</sup>+1):472  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>) : δ 0.82(3H, d, J=6.6Hz), 0.93(3H,d,J=6.6Hz), 1.29(3H,d, J=6.3Hz), 1.38(9H,s), 2.03-2.80(11H,m), 2.20(3H,s), 3.00-3.14(1H,m), 4.33~4.40(1H,m), 5.64(1H,d,J=7.7Hz), 6.68(1H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 6.95~7.18(5H,m)

Compound of which yielded amount was 0.226 g with HPLC retention time of 22.5 min.  
EI-MS(M<sup>+</sup>):471  
<sup>1</sup>H-NMR(CDCl<sub>3</sub>): δ 0.68 and 0.95(6H, d, J=6.6Hz), 1.15(3H,d, J=6.6Hz), 1.37(9H,s), 2.01-2.17(1H,m), 2.21(3H,s), 2.32-2.49(4H,m), 2.64-2.72(3H,m), 3.08-3.10(1H,m), 4.22-4.32(1H,q,J=2.5Hz), 5.60(1H,d,J=6.8Hz), 6.65 and 6.84(2H,d,J=7.9Hz), 6.94-7.00(3H,dd,J=6.3,11.2Hz), 7.13-7.18(2H,m)

Table D-62

## Example 76

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'			
Ac		H		Me			
Reaction 5							
Compound I-f5:g	Ac <sub>2</sub> O ml	DMAP ml	pyridine ml	Reaction time hr	Column. sol	Product	Amount g
0.630	3.00	0.21	4.50	16	H:EA:MC 3:2:2	I-h5	0.560
Reaction 6							
Compound I-h5:g	NaOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g	
0.540	2.00	4.00	1	Not purified	I-i5	0.430	
Reaction 7							
Compound I-i5:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol	Amount g	HPLC min	
0.430	2.00	2.00	1	MC:M:H 10:1:1	0.185	22.5	
EI-MS(M <sup>+</sup> +1):500							
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ) : δ 0.70(3H, d, J=5.6Hz), 0.84(3H,d, J=6.6Hz), 1.05(3H,d, J=6.6Hz), 1.37(9H,s), 1.78-1.96(2H,m), 1.90(3H,s), 2.43-2.74(4H,m), 3.07-3.32(2H,m), 3.46-3.56(1H,m), 3.59(1H,d,J=14.5Hz), 4.10-4.72(3H,m), 4.71(2H,s), 6.18-6.22(2H,br), 6.63-6.78(2H,m), 6.95-7.18(5H,m)							

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Table D-63

## Example 77

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-  
N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-  
5 hydroxymethylethyl)-N,3-dimethylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
Me		Me		CH <sub>2</sub> OH				
Reaction 1								
Compound T23:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.928	1.470	1.497	1.64	39	15	H:EA:M 2:3:1	I-d6	1.170
Reaction 2								
Compound I-d6:g	Pd-C g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g		
1.170	0.220	25	1	Not purified	I-e6	0.836		
Reaction 3								
Compound I-e6:g	Compound P5:g	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.836	0.997	0.329	0.28	25	1	MC:M:H 15:1:1	I-f6	1.200
Reaction 4								
Compound I-f6:g	HCHO ml	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.530	0.400	0.119	0.10	9	2	H:ACT 2:1:	I-g6	0.341
Reaction 7								
Compound I-g6:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol	Amount g	HPLC min		
0.225	2.5	3	1	CH:M:N 300:10:1	0.100	24.3		
EI-MS(M <sup>+</sup> ):471								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.12, 0.79, 0.84 and 0.98(6H, d, J=6.6-6.8Hz), 1.20(9H, s), 2.02-3.00(10H, m), 2.18 and 2.58(3H, s), 2.84 and 2.87(3H, s), 3.61-3.82(3H, m), 4.01-4.11 and 4.89-4.97(1H, m), 6.52 and 6.63(2H, d, J=8.1Hz), 6.72 and 6.89(1H, d, J=7.9Hz), 6.93-7.14(4H, m)								

Table D-64

## Example 78

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-

5 hydroxyphenyl)ethyl)-3-methylbutanamide

R <sub>32</sub>		R <sub>33</sub>		R'				
Me		H		CH <sub>2</sub> NH <sub>2</sub>				
Reaction 1								
Compound T22:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.89	0.90	0.92	0.89	13	20	MC:M:N 100:3:0.1	I-d7	1.40
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.80(3H,d,J=6.6Hz), 0.91(3H,d,J=6.6Hz), 1.37(9H,s), 1.42(9H,s), 2.00-2.15(1H,m), 2.55-2.90(2H,m), 3.10-3.30(2H,m), 3.90-4.20(2H,m), 4.80-4.90(1H,m), 5.11(2H,brs), 5.20-5.40(1H,m), 6.35-6.50(1H,m), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd, J=1.3,7.9Hz), 7.02(1H,1.3Hz), 7.36(5H,brs)								
Reaction 2								
Compound I-d7:g	Pd-C g	MeOH ml	Reaction time hr		Column. sol	Product	Amount g	
1.40	0.40	40	16		MC:M:N 100:5:0.1	I-e7	0.89	
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.56(3H,d,J=6.9Hz), 0.88(3H,d,J=6.9Hz), 1.38(9H,s), 1.43(9H,s), 2.10-2.30(1H,m), 2.65-2.85(2H,m), 3.15-3.35(3H,m), 4.15-4.30(1H,m), 4.95-5.05(1H,m), 6.62(1H,d,J=7.9Hz), 6.88(1H,dd, J=2.0,7.9Hz), 7.01(1H,d,J=2.0Hz), 7.43(1H,d,J=8.3Hz)								

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Table D-65

Example 78 (Continued from Table D-64)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-

5 hydroxyphenyl)ethyl)-3-methylbutanamide

Reaction 3								
Compound I -e7:g	Compound P5:g	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
1.02	1.07	0.28	0.15	26	1	EA:H 1:2	I-f7	1.41
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.70(3H,d,J=6.6Hz), 0.82(3H,d,J=6.6Hz), 1.37(9H,s), 1.39(9H,s), 1.44(9H,s), 1.80-2.00(1H,m), 2.20-2.50(1H,m), 2.60-2.90(6H,m), 3.10-3.40(2H,m), 3.70-3.90(1H,m), 4.20-4.30(1H,m), 4.60-4.80(1H,m), 4.95-5.10(1H,m), 6.60(1H,d,J=7.9Hz), 6.85-7.30(6H,m)								
Reaction 4								
Compound I -f7:g	HCHO ml	NaBH <sub>3</sub> CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.75	0.48	0.14	0.13	11	1	EA:H 1:2	I-g7	0.76
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): 0.83(3H,d,J=6.6Hz), 0.93(3H,d,J=6.6Hz), 1.36(9H,s), 1.41(18H,s), 1.90-3.10(10H,m), 3.10-3.30(2H,m), 3.60-3.80(1H,m), 4.40-4.60(1H,m), 4.60-4.80(1H,m), 4.90-5.05(1H,m), 6.10-6.20(1H,m), 6.30-6.40(1H,m), 6.63(1H,d,J=7.9Hz), 6.85-7.25(6H,m)								

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Table D-66

Example 78 (Continued from Table D-55)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Reaction 7						
Compound I-g7:g	TFA ml	CH <sub>2</sub> Cl <sub>2</sub> ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.70	10	0	1	MC:M:N 100:10:1	0.46	17.7
EI-MS(M <sup>+</sup> ):486 <sup>1</sup> H-NMR(CDCl <sub>3</sub> ):δ 0.83(3H,d,J=6.6Hz), 0.95(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.90(10H,m), 2.19(3H,s), 2.95-3.10(1H,m), 4.20-4.35(1H,m), 6.06(1H,d,J=8.3Hz), 6.62(1H,d,J=7.9Hz), 6.87(1H,dd,J=1.7,7.9Hz), 6.94-7.15(5H,m)						

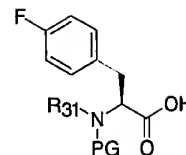
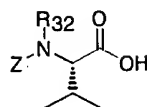
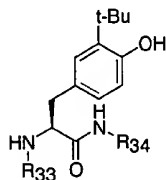
Examples 101-121 were carried out according to Scheme 3, Examples 121-131 were carried out according to Scheme 4, Example 132 was carried out according to Scheme 5, Examples 133-135 were carried out according to Scheme 6, Example 136 was carried out according to Scheme 7, Example 137 was carried out according to Scheme 8, Examples 138-165 were carried out according to Scheme 9, Examples 166 and 176 were carried out according to Scheme 10, Examples 167-171 were carried out according to Scheme 11, Examples 172 and 173 were carried out according to Scheme 12, Example 174 was carried out according to Scheme 13, Example 175 was carried out according to the scheme 14, Examples 177-179 were carried out according to Scheme 15, Example 180 was carried out according to Scheme 16, Examples 181 and 182 were carried out according to Scheme 17 and Example 183 was

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2
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5 101-137 are shown in Table C-2.

Table C-2

Intermediates of Examples 101-137



5 T1: R33=H, R34=H

V1: R32=Me

P1: PG=Boc, R31=H

T3: R33=H, R34=Et

V2: R32=Et

P2: PG=Boc, R31=Me

T6: R33=Me, R34=Et

P3: PG=Z, R31=Et

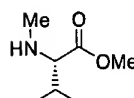
T9: R33=Et, R34=Et

P4: PG=Z, R31=H

T10: R33=H, R34=n-Pr

P5: PG=Z, R31=Me

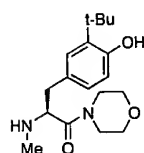
10 T11: R33=H, R34=i-Pr



V3

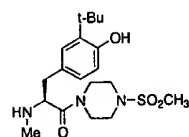
T12: R33=Me, R34=c-Pr

T16: R33=n-Pr, R34=H

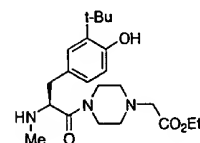


T13

15



T14



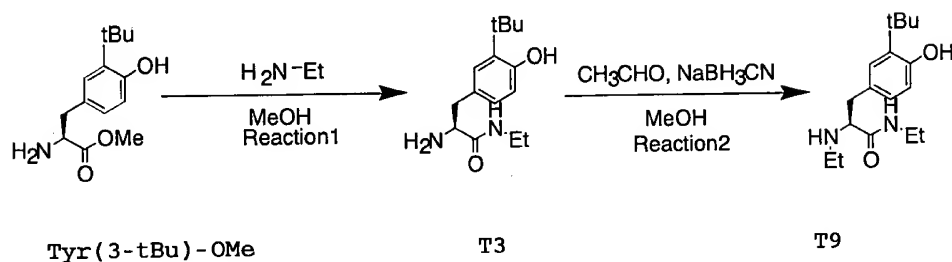
T15

Reference Example 16

Synthesis of Intermediates T3 and T9

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates T3 and T9



The process of synthesizing Intermediates T3 and T9

10 is explained below.

Reaction step 1) Synthesis of Intermediate T3

To a solution of Tyr(3-tBu)-OMe in methanol, a 70% aqueous ethylamine solution was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T3.

20 Reaction step 2) Synthesis of T9

To a solution of Compound T3 and acetaldehyde in methanol, NaBH<sub>3</sub>CN was slowly added dropwise. The reaction was stopped by the addition of an aqueous NaHCO<sub>3</sub> solution and the reaction mixture was concentrated under reduced pressure. The resultant was extracted with dichloromethane,

dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T9.

- 5           The result is shown in Table E-1. In Table E-1, indications "Reaction 1" and "Reaction 2" means Reaction step 1 and Reaction step 2, "Reaction time" means stirring time, "Column sol." means the eluting solvent for silica gel column chromatography, "Product" means the obtained product and "Amount" means the yielded amount of the product. The same manner is applied to the subsequent Tables.
- 10

Table E-1

- 15   Intermediates T3 (Tyr(3-tBu)-NH<sub>2</sub>Et) and T9 (N-Et-Tyr(3-tBu)-NH<sub>2</sub>Et)

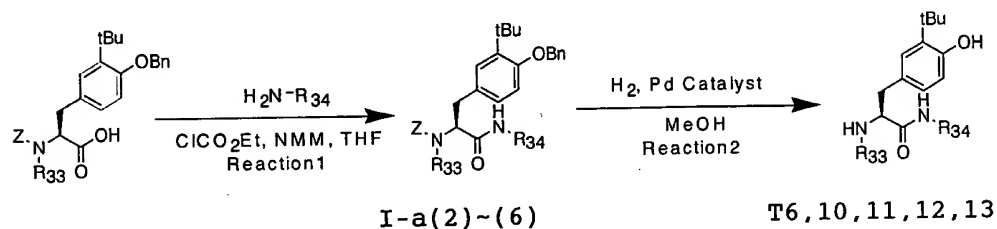
Reaction1						
Tyr(3-tBu)-OMe (g)	Ethyl amine (ml)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
14.000	168.00	56.00	18	nHx:EA=1:1	T3	12.810
Reaction2						
Compound T3(g)	CH <sub>3</sub> CHO (ml)	NaBH <sub>3</sub> CN (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
12.810	2.98	3.350	100.00	0.5	MC:MeOH =20:1	8.130

Reference Example 17

Synthesis of Intermediates T6, T10, T11, T12 and T13

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates T6, T10, T11, T12 and T13



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R<sub>33</sub> and R<sub>34</sub> in the above reaction scheme indicate  
10 substituents shown in Tables E-2 to E-6.

The process of synthesizing Intermediates is explained below.

Reaction step 1)

15 To solutions of Z-N-Me-Tyr(O-Bn, 3-tBu)-OH and ethyl chloroformate in THF, NMM was added. The mixture was stirred at room temperature and mixed with solutions of alkyl amines in THF. The mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine,  
20 dried over anhydrous magnesium and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a(2) to I-a(6).

Reaction step 2)

25 To solutions of Compounds I-a(2) to I-a(6) in

methanol, palladium hydroxide/carbon was added and stirred at room temperature in a hydrogen atmosphere. After filtering reaction mixtures, filtrates were concentrated under reduced pressure and the thus obtained residues were  
5 subjected to silica gel column chromatography, giving Compounds T6, T10, T11, T12 and T13. The results are shown in Tables E-2 to E-6.

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Table E-2

Intermediate T6

N-Me-Tyr(3-tBu)-NH<sub>2</sub>Et

R33					R34			
Me					Et			
Reaction 1								
Z-N-Me-Tyr(O-Bn, 3-tBu)-OH (g)	Ethylamine (ml)	ClCO <sub>2</sub> Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
11.300	118.80	3.40	3.90	230.00	6	nHx:EA =2:1	I-a(2)	8.400
Reaction 2								
Compound I-a(2) (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
6.200	0.600	120.00	3		MC:MeOH =20:1		3.600	

5

Table E-3

Intermediate T10

Tyr(3-tBu)-NH-n-Pr

R33					R34			
H					n-Pr			
Reaction 1								
Z-N-Me-Tyr(O-Bn, 3-tBu)-OH (g)	n-Propylamine (mL)	ClCO <sub>2</sub> Et (mL)	NMM (mL)	THF (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.100	1.40	0.57	0.66	30.00	2	nHx:EA:MC =1:3:1	I-a(3)	1.150
Reaction 2								
Compound I-a(3) (g)	Pd(OH) <sub>2</sub> (g)	MeOH (mL)	Reaction time (hr)		Column sol.		Amount (g)	
1.150	0.200	30.00	2		MC:MeOH =20:1		0.580	

10



Table E-4

Intermediate T11

Tyr(3-tBu)-NH-i-Pr

R33				R34				
H				i-Pr				
Reaction1								
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	i-Propyl amine (ml)	ClCO <sub>2</sub> Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	0.72	0.54	0.46	15.00	0.6	nHx:EA=2:1	I-a(4)	1.200
Reaction2								
Compound I-a(4) (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.200	0.500	30.00	3.5		EA:MeOH=20:1		0.660	

5

Table E-5

Intermediate T12

N-Me-Tyr(3-tBu)-NH-c-Pr

R33				R34				
Me				c-Pr				
Reaction 1								
Z-NMe-Tyr(O-Bn,3-tBu)-CH (g)	c-Propyl-amine (ml)	ClCO <sub>2</sub> Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.20	0.46	0.40	30.00	2	nHx:EA:MC =1:3:1	I-a(5)	1.050
Reaction 2								
Compound I-a(5) (g)	Pd(CH <sub>3</sub> ) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.050	0.200	30.00	2		MC:MeOH =20:1		0.500	

10

Intermediate P5 was synthesized according to a similar method described in Reference Example 7.

Table E-6

Intermediate T13

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-morpholin-4-ylpropan-1-one

R33					R34				
Me					morpholine				
Reaction 1									
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	morpholine (g)	ClCO <sub>2</sub> Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.200	0.660	0.27	0.42	15.00	20	nHx:EA =1:1	I-a(6)	1.200	
Reaction 2									
Compound I-a(6) (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)		
1.200	0.300	20.00	20		MC:MeOH =20:1		0.600		

5

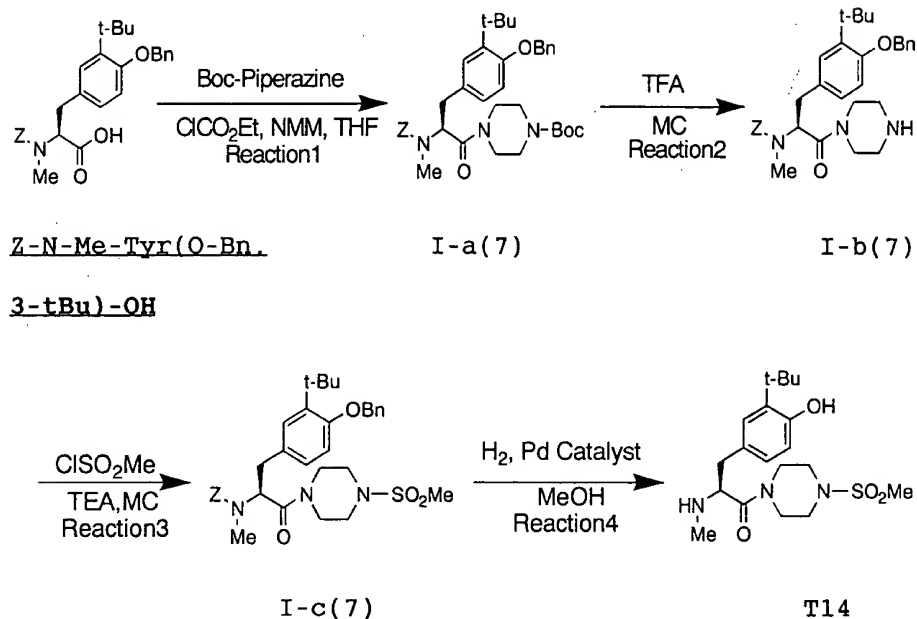
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Reference Example 18

Synthesis of Intermediate T14

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate T14



The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

- 15 Compound I-a(7) was obtained according to the method described in Reaction step 1 of Reference Example 17.

Reaction step 2)

To a solution of Compound I-a(7) in dichloromethane, TFA was added under cooling and stirred at room temperature.

- 20 The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and

filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b(7).

Reaction step 3)

- 5           To a solution of Compound I-b(7) and  $\text{ClSO}_2\text{Me}$  in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

- 10          The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c(7).

Reaction step 4)

- Compound T14 was obtained according to the method  
15          described in Reaction step 2 of Reference Example 17.  
Result is shown in Table E-7.

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25

Table E-7

Intermediate T14

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-[4-(methylsulfonyl)piperazineyl]propane-1-one

Reaction 1								
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Boc-piperazine (g)	ClCO <sub>2</sub> Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	0.700	0.36	0.42	15.00	20	nHx:EA=1:1	I-a(7)	1.900
Reaction 2								
Compound I-a(7) (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.900	5.00	20.00	4	MC:MeOH=20:1		I-b(7)	1.400	
Reaction 3								
Compound I-b(7) (g)	ClSO <sub>2</sub> Me (ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.400	0.46	0.82	20.00	2	MC:MeOH =20:1	I-c(7)	1.500	
Reaction 4								
Compound I-c(7) (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.500	0.300	20.00	20		MC:MeOH =20:1		0.900	

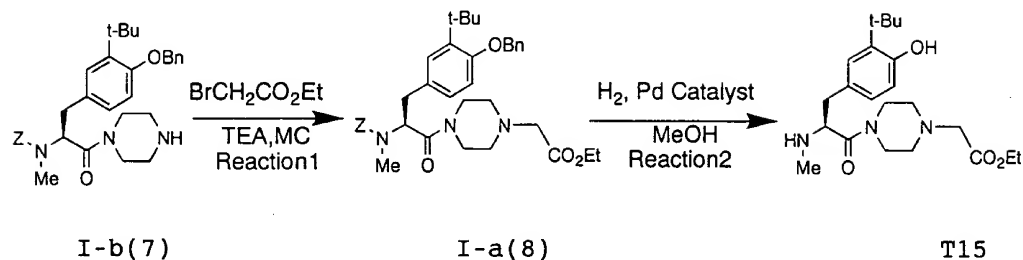
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Reference Example 19

Synthesis of Intermediate T15

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate T15



The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

To a solution of Compound I-b(7) and ethyl 2-bromoacetate in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a(8).

Reaction step 2)

Compound T15 was obtained according to the method described in Reaction step 2 of Reference Example 17. Result is shown in Table E-8.

Table E-8

Intermediate T15

Ethyl 2-(4-((2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)propanoyl)piperazinyl)acetate

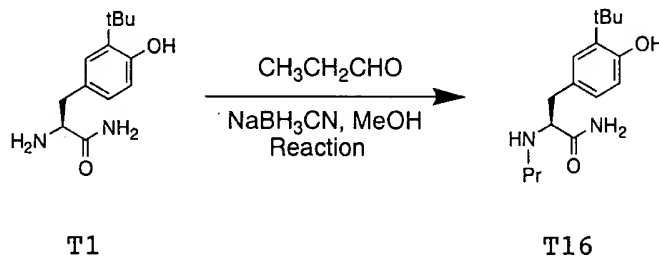
Reaction1							
Compound I-b(7) (g)	Ethyl bromo acetate(ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.970	0.30	0.40	17.00	4	nHex:EA=3:1	I-a(8)	1.000
Reaction2							
Compound I-a(8) (g)	Pd(OH) <sub>2</sub> (g)		MeOH (ml)		Reaction time (hr)		Amount (g)
1.000	0.300		16.00		1		0.643

Reference Example 20

Synthesis of Intermediate T16

The synthesis scheme is shown below.

Synthesis scheme of Intermediate T16



The process of synthesizing Intermediate T16 is explained below.

To a solution of Compound T1 in methanol, propionaldehyde was added, stirred at room temperature for 30 min., mixed with NaBH<sub>3</sub>CN and stirred for 2 hours. The reaction mixture was mixed with a saturated aqueous NH<sub>4</sub>Cl solution, extracted with ethyl acetate, washed with

saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T16.

5 Result is shown in Table E-9.

Table E-9

Intermediate T16

N-Pr-Tyr(3-tBu)-NH<sub>2</sub>

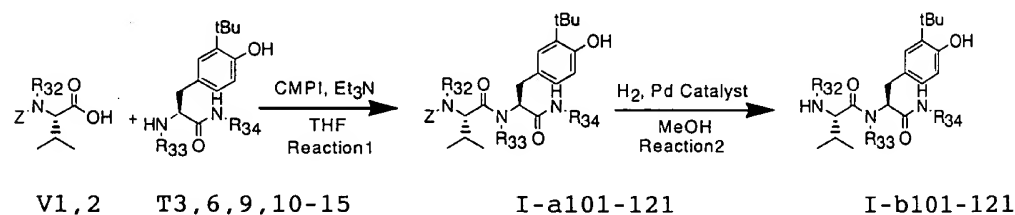
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Reaction						
Compound T1 (g)	CH <sub>3</sub> CH <sub>2</sub> CHO (ml)	NaBH <sub>3</sub> CN (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	1.34	1.170	70.00	2	nHx:EA=1:2	1.580

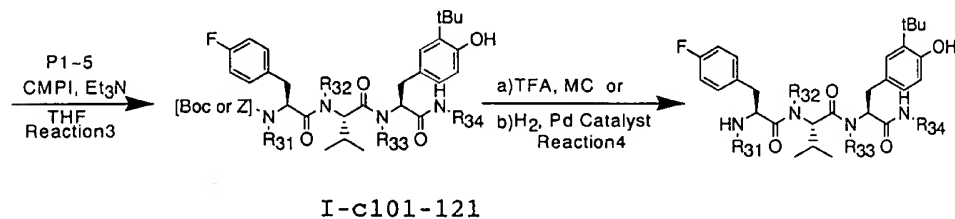
Scheme 3 shows the synthesis process of Examples 101-121.

15

Scheme 3: Synthesis process of Examples 101-121



20



R<sub>31</sub>, R<sub>32</sub>, R<sub>33</sub> and R<sub>34</sub> in the above reaction scheme



indicate substituents shown in Tables D-101 to D-121.

The synthesis process in scheme 3 is explained below.

Reaction step 1)

5           To solutions of Compounds T, Compounds V and CMPI in THF, TEA was added under cooling and stirred at room temperature. The mixtures were mixed with water, extracted with ethyl acetate, washed with a saturated aqueous  $\text{NaHCO}_3$  solution, dried over anhydrous magnesium sulfate and  
10           filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a101 to I-a121.

15           Reaction step 2)

            To solutions of Compounds I-a101 to I-a121 in methanol, Pd/C was added and stirred at room temperature in a hydrogen atmosphere. After filtering off the Pd/C, the filtrates were concentrated under reduced pressure and the  
20           thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-b101 to I-b121.

Reaction step 3)

            To solutions of Compounds I-b101 to I-b121, P1 to P5  
25           and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-c101 to I-c121.

5 Reaction step 4-a)

To solutions of Compounds I-c101 to I-c121 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were neutralized by the addition of a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving the titled compounds.

15

Reaction step 4-b)

To solutions of Compounds I-c101 to I-c121 in methanol,  $\text{Pd/C}$  or  $\text{Pd(OH)}_2$  was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the  $\text{Pd/C}$  or  $\text{Pd(OH)}_2$ , the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 3 are shown in Tables D-101 to D-121.

Table D-101

## Example 101

## Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHet

R31		R32		R33		R34		
H		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a101	5.220
Reaction2								
Compound I-a101(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1	I-b101		2.200	
Reaction3								
Compound I-b101(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.500	0.600	0.50	15.00	20	nHx:EA =1:1	I-c101	0.830
Reaction4-b								
Compound I-c101(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.830	0.100	10.00	20	MC:MeOH =10:1		0.170	18.42	
ESI-MS(M <sup>+</sup> +1): 557								
1H-NMR(CDCI <sub>3</sub> ): δ 0.59-1.05(9H,m), 1.37(9H, s), 2.25-2.39(1H, m), 2.58-3.24(9H, m), 3.58-3.97(2H,m), 4.44-4.62(1H,m), 5.59-5.77(1H,m), 6.60-7.72(8H,m), 9.03 and 9.06(1H, d, J=7.9Hz)								

Table D-102

## Example 102

N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHet

R31		R32		R33		R34		
Me		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a102	5.220
Reaction2								
Compound I-a102(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1		I-b102	2.200	
Reaction3								
Compound I-b102(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.000	1.310	0.72	20.00	20	nHx:EA =1:1	I-c102	1.560
Reaction4-a								
Compound I-c102(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.500	1.70	10.00	4	MC:MeOH =10:1		0.28	18.73	
ESI-MS(M <sup>+</sup> +1): 557								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.57, 0.79, 0.92 and 1.00(9H, d and m, J=6.3-6.8Hz), 1.34and 1.38(9H, s), 2.25, 2.40 and 2.58, 2.65(6H, s), 2.05-2.40(1H, m), 2.67-3.25(6H, m), 3.55 nad 3.68(1H,m), 3.84, 4.40 and 4.55(2H, d and m, J=10.9Hz), 5.56 and 5.72(1H,m), 6.65-7.17(8H,m), 9.15 and 9.18 (1H, d, J=8.2Hz)								

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Table D-103

## Example 103

N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Et		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a103	5.220
Reaction2								
Compound I-a103(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1		I-b103	2.200	
Reaction3								
Compound I-b103(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.670	1.050	0.57	20.00	20	nHx:EA =1:1	I-c103	0.800
Reaction4-b								
Compound I-c103(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.800	0.100	10.00	20	MC:MeOH =10:1		0.220	19.27	
ESI-MS(M <sup>+</sup> +1): 571								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.42-1.20(12H,m), 1.35 and 1.39(9H, s), 2.05-2.26(1H, m), 2.31-2.54(1H, m),2.40 and 2.50(3H,s), 2.62-3.26(6H,m), 3.62-3.80(1H,m),4.34-4.58(1H,m), 5.79-5.87(1H, m), 6.60-7.04(7H, m)								

Table D-104

## Example 104

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
H		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a104	4.200
Reaction2								
Compound I-a104 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH =20:1		I-b104	3.900	
Reaction3								
Compound I-b104(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.600	1.300	0.90	30.00	18	nHx:EA =1:2	I-c104	0.920
Reaction4-b								
Compound I-c104(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.920	0.100	10.00	3	MC:MeOH =20:1		0.210	19.57	
ESI-MS(M <sup>+</sup> +1): 557								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.56, 0.77, 0.79 and 0.92(6H, d, J=6.4-6.7Hz), 1.01-1.12(3H, m), 1.38 and 1.33(9H, s), 2.19-2.68(2H, m), 2.52 and 2.83(3H, s), 2.68-3.42(4H, m), 3.00 and 3.02(3H, s), 3.65-3.87(1H, m), 4.90-5.11 and 5.35-5.47(2H, m), 5.95-6.08(1H, m), 6.36 and 6.62(1H, d, J=7.8-7.9Hz), 6.68-7.16(6H, m)								

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Table D-105

## Example 105

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Me		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a105	4.200
Reaction2								
Compound I-a105 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH =20:1		I-b105	3.900	
Reaction3								
Compound I-b105 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.480	1.300	0.90	30.00	18	nHx:EA =1:2	I-c105	1.020
Reaction4-a								
Compound I-c105 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.020	2.30	23.00	6	MC:MeOH =20:1		0.200	20.213	
ESI-MS(M <sup>+</sup> +1): 571								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.63, 0.80, 0.81 and 0.92(6H, d, J=6.4-6.9Hz), 1.06(3H, t, J=7.3Hz), 1.34 and 1.39(9H, s), 2.13-2.33(1H, m), 2.22 and 2.25(3H, s), 2.53 and 2.82(3H s), 2.54(1H, s), 2.60-2.70(2H, m), 2.74-2.90(1H, m), 2.95 and 3.06(3H, s), 3.45 and 3.59(1H, t, J=5-6.8Hz), 5.07 and 5.15(1H, d, J=10.6-10.9Hz), 5.05 and 5.38(1H, dd, J=8.1-9.3, 6.1-6.8Hz), 6.0(1H, t, J=5.0Hz), 6.40 and 6.61(1H, d, J=8.0Hz), 6.75(3H, m), 7.02-7.18(3H, m)								

Table D-106

## Example 106

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>Et

R31		R32		R33		R34		
Et		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a106	4.200
Reaction2								
Compound I-a106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH= 20:1		I-b106	3.900	
Reaction3								
Compound I-b106 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.740	1.300	0.90	30.00	15	nHx:EA =1:2	I-c106	1.050
Reaction4-b								
Compound I-c106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.050	0.100	14.00	3	MC:MeOH= 20:1		0.200	20.950	
ESI-MS(M <sup>+</sup> +1): 585								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.65, 0.79, 0.8 and 0.91(6H, d, J=6.0Hz), 0.97-1.08(6H, m),1.34 and 1.39(9H, s), 2.21-2.38(2H, m), 2.46-2.59(2H, m), 2.61-2.9(2H, m),2.5 and 2.75(3H, s),2.96 and 3.06(3H, s), 3.17-3.46(2H, m), 3.55 and 3.68(1H, t, J=7.0Hz), 5.01-5.36(2H, m), 5.97-6.0(1H, m), 6.41 and 6.59(1H, d, J=8.0Hz), 6.79-6.98(3H, m), 7.04-7.17(3H, m)								

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### Example 107

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34	
H		Me		Et		Et	
Reaction1							
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a107 3.030
Reaction2							
Compound I-a107(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)
8.000	1.200	50.00	15	MC:MeOH = 10:1		I-b107	5.000
Reaction3							
Compound I-b107(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product Amount (g)
0.800	0.815	0.606	0.40	30.00	18	nHx:EA=1:2	I-c107 1.040
Reaction4-b							
Compound I-c107(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min
1.047	0.156	20.00	3.5	MC:MeOH =20:1		0.252	21.09
ESI-MS(M <sup>+</sup> +1):571							
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.74, 0.80 and 0.92(6H, d, J=7.0-7.9Hz), 0.97-1.20(6H, m), 1.32 and 1.36(9H, s), 2.20-3.13(5H, m), 2.74 and 3.05(3H, s), 3.15-3.35(3H, m), 3.35-3.95(3H, m), 4.92-5.10(2H, m), 6.44 and 6.73(1H, d, J=8.8Hz), 6.50(3/5H, m), 6.75(3/5H, dd, J=7.9, 1.7Hz), 6.90-7.29(29/5H, m)							

Table D-108

## Example 108

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Me		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a108	3.030
Reaction2								
Compound I-a108(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15.00	MC:MeOH = 10:1		I-b108	5.000	
Reaction3								
Compound I-b108(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.022	1.130	0.966	0.70	20.00	19	nHx:EA=1:2	I-c108	1.590
Reaction4-a								
Compound I-c108(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.590	1.80	10.00	3	MC:MeOH =20:1		0.251	21.54	
ESI-MS(M <sup>+</sup> +1):585								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.78-0.90 and 0.95(6H, m and d, J=7.9Hz), 0.97-1.10(3H, m), 1.10 and 1.22(3H, m),1.31 and 1.39(9H, s), 2.21-2.25(3H, s), 2.19-2.40(1H, m),2.55-3.35(7H, m), 2.69 and 2.72(3H, s), 3.42-3.75(3H, m),4.95-5.10(1H, m),5.12(1H, d, J=10.6Hz),6.44 and 6.58(1H, d, J=8.8Hz), 6.50(3/5H,m), 6.79(3/5H, dd, J=8.1, 2.5Hz), 6.88-7.00(12/5H, m), 7.05-7.20(12/5H, m) 7.27(1H, brs)								

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Table D-109

## Example 109

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Et		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a109	3.030
Reaction2								
Compound I-a109(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15	MC:MeOH = 10:1		I-b109	5.000	
Reaction3								
Compound I-b109(g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.819	0.606	0.40	16.00	18	nHx:EA=1:2	I-c109	1.000
Reaction4-b								
Compound I-c109(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.000	0.150	20.00	15	MC:MeOH =20:1		0.127	21.920	
ESI-MS(M <sup>+</sup> +1):599								
1H-NMR(CDC1 <sub>3</sub> ):(two rotamers) δ 0.78-0.88 and 0.92(6H, m and d, J=7.4Hz), 0.98-1.18(6H, m), 1.20(3H, q, J=6.4Hz), 1.34 and 1.38(9H, s), 2.20-2.43(2H, m),2.43-3.35(8H, m),2.68 and 2.80(3H, s), 3.42-3.78(3H, m), 4.90-5.12(1H, m), 5.12(1H, d, J=10.6Hz), 6.42 and 6.58(1H, d, J=15.3Hz), 6.50(1/3H,m), 6.80(2/3H, dd, J=8.8, 2.1Hz), 6.85-7.00(3H, m),7.05-7.17(10/3H, m),7.30(2/3H, brs)								

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Table D-110

## Example 110

Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
H		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA=1:1	I-a110	9.540
Reaction2								
Compound I-a110 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.000	0.600	60.00	20	MC:MeOH =20:1		I-b110	3.570	
Reaction3								
Compound I-b110(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	1.500	2.000	1.00	20.00	20	nHx:EA =1:1	I-c110	0.400
Reaction4-a								
Compound I-c110(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.60	3.00	4	MC:MeOH =20:1		0.200	20.25	
ESI-MS(M <sup>+</sup> +1): 557								
1H-NMR(CDCl <sub>3</sub> ): δ 0.62-1.16(12H,m), 1.38(9H, s), 2.25-2.45(1H, m), 2.62-3.86(9H, m), 3.92 and 3.95(1H, d, J=10.0Hz), 4.44-5.56(1H, m), 5.67-5.90(1H, m), 6.60-7.20(7H, m), 9.05 and 9.08(1H, d, J=7.8Hz)								

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Table D-111

## Example 111

N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Me		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a111	9.540
Reaction2								
Compound I-a111 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.000	0.600	60.00	20	MC:MeOH =20:1		I-b111	3.570	
Reaction3								
Compound I-b111(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.600	2.000	1.00	20.00	20	nHx:EA =1:1	I-c111	0.400
Reaction4-a								
Compound I-c111(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.60	3.00	4	MC:MeOH =20:1		0.300	20.77	
ESI-MS(M <sup>+</sup> +1): 571								
1H-NMR(CDC <sub>3</sub> ): (two rotamers) δ 0.67 and 0.80-1.16(12H, d and m, J=6.8Hz), 1.37(9H, s), 2.30(3H, s), 2.35-2.39(1H, m), 2.79-3.22(8H, m), 3.53-3.59(1H, m), 4.04-4.15(1H, m), 4.39-4.46(1H, m), 5.73-5.77(1H, m), 6.61 and 6.64(1H, d, J=8.2Hz), 6.84-7.19(6H, m)								

Table D-112

Example 112

N-Et -Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Et		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a112	9.540
Reaction2								
Compound I-a112 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.200	0.600	60.00	20	MC:MeOH =20:1		I-b112	3.570	
Reaction3								
Compound I-b112(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.585	2.000	1.00	20.00	20	nHx:EA =1:1	I-c112	0.550
Reaction4-b								
Compound I-c112(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.050	4.00	20	MC:MeOH =30:1		0.098	21.090	
ESI-MS(M <sup>+</sup> +1): 585								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.48 and 0.71-1.31(15H, d and m, J=7.4Hz), 1.37(9H, s), 2.20-2.61(2H, m), 2.71-3.34(10H, m), 3.60-3.82(2H, m), 4.40-4.56(1H, m), 5.80-5.98(1H, m), 6.67-7.01(3H, m), 7.02-7.16(3H, m), 7.48 and 7.50(1H, d, J=6.8Hz), 8.73 and 8.76(1H,d, J=7.9Hz)								

Table D-113

## Example 113

Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
H		Et		Me		Et		
Reaction1								
Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a113	5.500
Reaction2								
Compound I-a113 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b113	3.200	
Reaction3								
Compound I-b113 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c113	0.320
Reaction4-a								
Compound I-c113 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.320	0.70	7.40	6	MC:MeOH =20:1		0.020	20.260	
ESI-MS(M <sup>+</sup> +1): 571								
1H-NMR(CDCl <sub>3</sub> ) δ 0.36-0.96(8H,m), 0.98-1.10(4H,m), 1.35 and 1.39(9H,s), 2.28-2.41(1H,m), 2.84 and 3.04(3H,s), 2.55-3.39(8H,m), 3.68-3.78(1H,m), 4.90-5.32(2H,m) 6.45 and 6.65(1H, d, J=6.0Hz), 6.77-7.23(6H,m)								

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Table D-114

## Example 114

N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
Me		Et		Me		Et		
Reaction1								
CompoundT6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a114	5.500
Reaction2								
Compound I-a114 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b114	3.200	
Reaction3								
Compound I-b114 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	20	nHx:EA =1:2	I-c114	0.300
Reaction4-a								
Compound I-c114 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.300	0.70	6.80	6	MC:MeOH =20:1		0.030	20.880	
ESI-MS(M <sup>+</sup> +1): 585								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.51, 0.81, 0.87 and 0.91(6H, d, J=6.3-6.9Hz), 0.94, 1.04 and 1.17(6H, t, J=3.6Hz), 1.34 and 1.39(9H,s), 2.18-2.62(1H, m), 2.38(3H, s), 2.57-2.88 (3H, m), 2.91-3.38(5H,m), 2.94 and 3.06(3H,s), 3.49 and 3.57(1H, t, J=6.4-7.2Hz), 5.49-5.32 (2H,m), 6.02-6.1 and 6.53-6.59(1H, m), 6.45 and 6.64(1H, d, J=8.0Hz),6.76-7.03(3H, m),7.08 -7.19(3H, m)								

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Table D-115

## Example 115

N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NH<sub>2</sub>Et

R31		R32		R33		R34		
Et		Et		Me		Et		
Reaction1								
Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a115	5.500
Reaction2								
Compound I-a115 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b115	3.200	
Reaction3								
Compound I-b115 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c115	0.300
Reaction4-b								
Compound (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.300	0.030	4.00	3	MC:MeOH =20:1		0.040	21.59	
ESI-MS(M <sup>+</sup> +1): 599								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.38-1.17(15H,m), 1.34, 1.36 and 1.38(9H,s), 3.38-2.12 (1H,m), 3.55(1H, t, J=6.3Hz), 3.47-3.72(1H, m), 4.88-5.37(2H, m), 5.79-6.09 and 6.63-6.7(1H, m), 6.42 and 6.62(1H, dd, J=8.3,7.4Hz), 7.05-7.22(6H,m)								

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Table D-116

## Example 116

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>

R31		R32		R33		R34		
H		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a116	3.030
Reaction2								
Compound I-a116(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	MC:MeOH = 10:1		I-b116	2.24	
Reaction3								
Compound I-b116(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.680	0.549	0.40	12.00	18	nHx:EA=1:1	I-c116	0.200
Reaction4-b								
Compound I-c116(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.200	0.030	4.00	3	MC:MeOH =20:1		0.053	21.59	
ESI-MS(M <sup>+</sup> +1):585								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.60 and 0.78-1.30(15H, d and m, J=7.9Hz), 1.34 and 1.38(9H, s), 2.22-2.50(1H, m), 2.52-3.00(3H, m), 3.00-3.54(6H, m), 3.54-3.94(2H, m), 4.82-5.05(1H, m), 5.10(1H, m), 6.45-6.70(2H, m), 6.80(3/4H, m), 6.91-7.25(21/4H, m)								

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Table D-117

## Example 117

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH<sub>2</sub>t

R1		R2		R3		R4		
Me		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a117	3.030
Reaction2								
Compound I-a117(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	M C:MeOH = 10:1		I-b117	2.240	
Reaction3								
Compound I-b117(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.845	0.681	0.585	0.40	16.00	48	nHx:EA=1:1	I-c117	0.378
Reaction4-a								
Compound I-c117(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.378	0.80	4.00	3	M C:MeOH =20:1		0.056	22.20	
ESI-MS(M <sup>+</sup> +1):599								
1H-NMR(CDC1 <sub>3</sub> ):(two rotamers) δ 0.75 and 0.83-1.10(10H, d and m, J=7.9Hz), 1.10-1.30(5H, m), 1.35 and 1.39(9H, s), 2.30 and 2.33(3H, s), 2.30-2.48(1H, m), 2.65-3.89(12H, m), 4.90 and 5.07(1H, m), 5.18 and 5.23(1H, d, J=9.7Hz), 6.48 and 6.58(1H, d, J=8.8Hz), 6.63(1/2H, m), 6.80(1H, dd, J= 8.1, 1.8Hz), 6.90-7.0(7/2H, m), 7.05(1/2H, d, J=1.7Hz), 7.06-7.20(5/2H, m)								

0909219 1430 61206360

Figure 1 consists of 12 sub-graphs, labeled (a) through (l), arranged in a 4x3 grid. Each graph plots the 'Rate of Polymerization' on the y-axis against a different factor on the x-axis. The factors are: (a) Time, (b) Temperature, (c) Concentration of monomer, (d) Concentration of initiator, (e) Concentration of catalyst, (f) Concentration of solvent, (g) Concentration of inhibitor, (h) Concentration of chain transfer agent, (i) Concentration of chain extender, (j) Concentration of chain terminator, (k) Concentration of chain transfer agent, and (l) Concentration of chain extender. The graphs show that the rate of polymerization is generally highest at low concentrations of inhibitors and chain transfer agents, and increases with increasing monomer and initiator concentrations.

Figure 1 consists of 12 sub-graphs labeled (a) through (l), each showing the rate of polymerization ( $R_p$ ) in g/hr on the y-axis against a different factor on the x-axis. The factors are: (a) Time, (b) Temperature, (c) Concentration of monomer, (d) Concentration of initiator, (e) Concentration of catalyst, (f) Concentration of solvent, (g) Concentration of inhibitor, (h) Concentration of chain transfer agent, (i) Concentration of chain extender, (j) Concentration of chain terminator, (k) Concentration of chain transfer agent, and (l) Concentration of chain extender. The graphs show that  $R_p$  generally increases with time, temperature, and monomer concentration, and decreases with increasing concentrations of inhibitors and chain transfer agents.

Figure 1 consists of 12 sub-graphs, labeled (a) through (l), each showing the relationship between a different factor and the rate of polymerization of methyl methacrylate. The y-axis for all graphs is 'Rate of Polymerization'. The x-axes represent different variables:

- (a) Time: Shows a linear increase in rate over time.
- (b) Temperature: Shows a peak in rate at an optimal temperature, with rates decreasing at higher and lower temperatures.
- (c) Concentration of monomer: Shows a linear increase in rate with increasing monomer concentration.
- (d) Concentration of initiator: Shows a linear increase in rate with increasing initiator concentration.
- (e) Concentration of catalyst: Shows a linear increase in rate with increasing catalyst concentration.
- (f) Concentration of solvent: Shows a linear decrease in rate as solvent concentration increases.
- (g) Concentration of inhibitor: Shows a linear decrease in rate as inhibitor concentration increases.
- (h) Concentration of chain transfer agent: Shows a linear decrease in rate as chain transfer agent concentration increases.
- (i) Concentration of stabilizer: Shows a linear decrease in rate as stabilizer concentration increases.
- (j) Concentration of surfactant: Shows a linear increase in rate with increasing surfactant concentration.
- (k) Concentration of plasticizer: Shows a linear decrease in rate as plasticizer concentration increases.
- (l) Concentration of filler: Shows a linear decrease in rate as filler concentration increases.

Figure 1 consists of 12 line graphs, labeled (a) through (l), arranged in a 4x3 grid. Each graph plots 'Log CFU/g' on the y-axis (ranging from 0 to 10) against 'Time (min)' on the x-axis (ranging from 0 to 120). The graphs show the effect of various chemical treatments on the growth of *E. coli* O157:H7. The treatments are: (a) 0.1% NaOCl, (b) 0.2% NaOCl, (c) 0.5% NaOCl, (d) 1.0% NaOCl, (e) 0.1% NaOCl + 0.1% NaOH, (f) 0.2% NaOCl + 0.1% NaOH, (g) 0.5% NaOCl + 0.1% NaOH, (h) 1.0% NaOCl + 0.1% NaOH, (i) 0.1% NaOCl + 0.1% NaOH + 0.1% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, (j) 0.2% NaOCl + 0.1% NaOH + 0.1% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, (k) 0.5% NaOCl + 0.1% NaOH + 0.1% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, and (l) 1.0% NaOCl + 0.1% NaOH + 0.1% Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>. The graphs show that higher concentrations of NaOCl and the addition of NaOH and Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> lead to faster and more complete inactivation of the bacteria.

Table D-119

## Example 119

Phe(4-F)-N-Me-Val-Tyr(3-t Bu)-NH-n-Pr

R31		R32		R33		R34		
H		Me		H		n-Pr		
Reaction1								
Compound Tl0(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.580	0.640	0.670	0.92	10.00	18	nHx:EA=1:1	I-a119	1.030
Reaction2								
Compound I-a119(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.030	0.200	10.00	2	MC:MeOH=15:1		I-b119	0.76	
Reaction3								
Compound I-b119(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	0.660	0.650	1.07	10.00	19	nHx:EA=1:2	I-c119	1.100
Reaction4-a								
Compound I-c119(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.100	6.66	13.30	2	MC:MeOH =15:1		0.210	20.10	
ESI-MS(M <sup>+</sup> +1):557								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.68-0.92(9H, m), 1.38 and 1.39(9H, s), 2.69 and 2.85 (3H, s), 1.37-3.20(7H, m), 3.62-3.90(1H, m), 3.93(1H, d, J=10.9Hz), 4.42-4.57(1H, m), 6.62-7.17(7H, m)								

Table D-120

## Example 120

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr

R31		R32		R33		R34		
H		Me		H		i-Pr		
Reaction1								
Compound T11 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.630	0.910	0.66	10.00	3	nHx:EA= 1:1	I-a120	1.210
Reaction2								
Compound I-a120 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.210	0.500	20.00	2	MC:MeOH =20:1		I-b120	0.900	
Reaction3								
Compound I-b120 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.900	0.650	0.880	0.64	15.00	3	nHx:EA =2:1	I-c120	1.300
Reaction4-a								
Compound I-c120 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.300	5.00	20.00	2	MC:MeOH = 25:1		0.960	19.99	
ESI-MS(M <sup>+</sup> +1):557								
1H-NMR(CDCI <sub>3</sub> ) : (two rotamers) δ 0.70-1.07(12H, m), 1.35 and 1.38(9H, s), 1.72(2H, brs), 2.29-2.37(1H, m), 2.72 and 2.83(3H, s), 2.52-2.74(4H, m), 3.60 and 3.81(1H, dd, J=8.2 , 3.0Hz), 3.85-3.98(2H, m), 4.42-4.60(1H, m), 5.48 and 5.69(1H, d, J=7.8Hz), 6.62-6.80(2H, m), 6.90-6.98(3H, m), 7.06-7.11(2H, m), 9.07(1H, d, J=8.2Hz)								

Table D-121

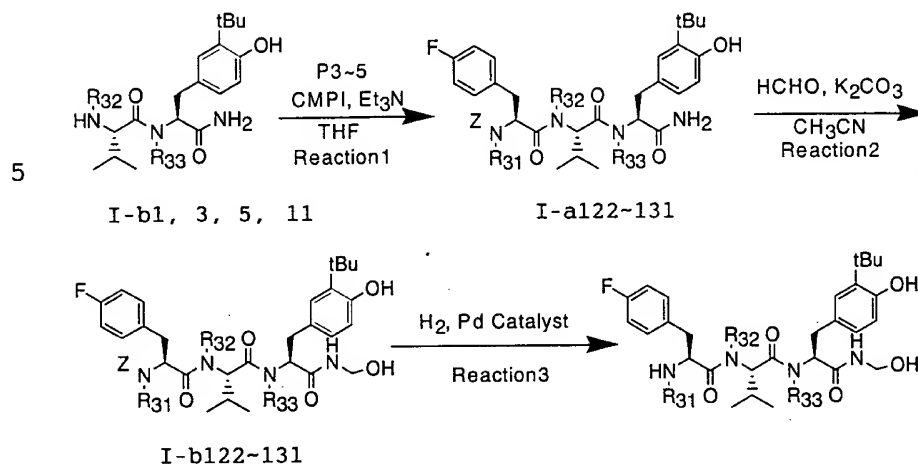
## Example 121

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr

R31		R32		R33		R34		
H		Me		Me		c-Pr		
Reaction1								
Compound T12(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.520	0.600	0.70	10.00	18	nHx:EA:MC =1:1:1	I-a121	0.850
Reaction2								
Compound I-a121(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.850	0.200	10.00	2	MC:MeOH=15:1		I-b121	0.400	
Reaction3								
Compound I-b121(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.540	0.550	0.57	10.00	19	nHx:EA:MC =1:3:1	I-c121	0.720
Reaction4-a								
Compound I-c121(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	3.30	6.60	2	MC:MeOH =15:1		0.210	18.12	
ESI-MS(M <sup>+</sup> +1):569								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.17-0.88(11H, m), 1.31 and 1.34(9H, s), 2.28, 2.63, 2.90 and 3.93(6H, s), 2.11-3.08 (6H, m), 4.43-5.26(3H, m), 6.48 and 6.61(1H, d, J=7.9Hz), 6.62-7.16(6H, m)								

Scheme 4 shows the synthesis process of Examples 122-131

Scheme 4: Synthesis process of Examples 122-131



10                       $R_{31}$ ,  $R_{32}$ , and  $R_{33}$  in the above reaction scheme indicate substituents shown in Tables D-122 to D-131.

The synthesis process in scheme 4 is explained below.  
Reaction step 1)

15                      To solutions of Compounds I-b1, I-b3, I-b5 and I-b11, Compounds P3 to P5 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous

20                      magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a122 to I-a131.



Reaction step 2)

To solutions of Compounds I-a122 to I-a131 in  $\text{CH}_3\text{CN}$ , 38%  $\text{HCHO}$  and an aqueous  $\text{K}_2\text{CO}_3$  solution were added and stirred at room temperature. The reaction mixtures were mixed with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compounds I-b122 to I-b131.

Reaction step 3)

To solutions of Compounds I-b122 to I-b131 in methanol,  $\text{Pd/C}$  was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the  $\text{Pd/C}$ , the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 4 are shown in Tables D-122 to D-131.

Table D-122

## Example 122

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
H			Me			H		
Reaction1								
Compound I-b1 (g)	CompoundP4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.760	0.610	0.56	40.00	4	nHc:EA=2:1	I-a122	1.000
Reaction2								
Compound I-a122(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.000	1.15	0.430	30.00	2	nHc:EA:MC =1:3:1	I-b122	0.900	
Reaction3								
Compound I-b122(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.900	0.140	13.00	2	EA:MeOH=15:1	0.560	15.91		
ESI-MS(M <sup>+</sup> +1):545								
1H-NMR(CDC <sub>3</sub> ) <sub>2</sub> (two rotamers) δ 0.69, 0.75, 0.83 and 0.90(6H, d, J=6.4-6.7Hz), 1.34 and 1.35(9H, s), 2.22-3.17(5H, m) 2.68 and 2.88(3H, s), 3.57 and 3.82(1H, dd, J=8.0-8.5, 5.5-6.0Hz), 4.51-4.74(3H, m), 6.61-9.02(8H, m)								

Table D-123

## Example 123

N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Me			Me			H		
Reaction1								
Compound I-b1 (g)	Compound P5(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.569	0.439	0.60	20.00	16	nHx:EA =1:1	I-a123	0.920
Reaction2								
Compound I-a123(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.910	1.00	0.380	25.00	2	nHx:EA =1:1	I-b123	0.927	
Reaction3								
Compound I-b123(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.270	0.100	10.00	1.5	EA:MeOH=30:1		0.228	16.04	
ESI-MS(M <sup>+</sup> +1):559								
1H-NMR(CDC <sub>3</sub> ) <sub>2</sub> :(two rotamers) δ 0.52, 0.77 and 0.89(6H, d, J=6.5-6.8Hz), 1.31 and 1.37(9H, s), 2.08-2.17(1H, m), 2.24 and 2.28(3H, s), 2.46 and 2.56(3H, s), 2.58-3.06(4H, m), 3.54-4.35(2H, m), 6.62-7.34(7H, m)								

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Table D-124

## Example 124

N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Et			Me			H		
Reaction1								
Compound I-b1 (g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.750	0.555	0.75	20.00	26	nHcEA=1:1	I-a124	0.987
Reaction2								
Compound I-a124(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.980	1.10	0.400	25.00	2	nHcEA=1:1	I-b124	0.911	
Reaction3								
Compound I-b124(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.910	0.200	15.00	3	MC:MeOH=15:1		0.250	16.36	
ESI-MS(M <sup>+</sup> +1):573								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.50, 0.75, 0.82 and 0.85(6H, d, J=6.3-7.0Hz), 0.98 and 1.12(3H, t, J=6.7Hz), 1.40 and 1.45(9H, s), 2.15(1H, m), 2.42 and 2.46(3H, s), 2.40(2H, m), 2.60-3.10(5H, m), 3.63(1H, dd, J=10.6, 6.0Hz), 4.50(1H, m), 4.70(2H, m), 6.70(4H, m), 6.90(1H, m), 7.00(1H, s), 7.12(1H, s), 7.20 and 7.40(1H, m), 8.75(1H, d, J=6.6Hz)								

Table D-125

## Example 125

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Me			Me			Me		
Reaction 1								
Compound I-b3(g)	Compound P5 (g)	OMPI (g)	TEA (mL)	THF (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	1.420	1.100	0.92	30.00	14	nHk:EA:MC =1:2:1	I-a125	1.800
Reaction 2								
Compound I-a125(g)	HCHO (mL)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.790	1.970	0.730	52.00	2	nHk:EA:MC =1:3:1	I-b125	1.500	
Reaction 3								
Compound I-b125(g)	Pd/C (g)	MeOH (mL)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
1.500	0.230	20.00	2	EA:MeOH=10:1	0.970	17.27		
ESI-MS(M <sup>+</sup> 1):573								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ):(two rotamers) d 0.57, 0.79 and 0.92(6H, d, J=6.3-6.8Hz), 1.34 and 1.38(9H, s), 2.22 and 2.25(3H, s), 2.29(1H, m), 2.52 and 2.82(3H, s), 2.55-2.89(3H, m), 2.92 and 3.04(3H, s), 3.20 and 3.39(1H, dd, J=11.1-14.1, 6.3-7.3Hz), 3.46 and 3.61(1H, t, J=6.8-6.9Hz), 4.59-4.76(2H, m), 5.03 and 5.14(1H, d, J=10.5Hz), 5.11 and 5.37(1H, dd, J=6.3, 9.7Hz), 6.39 and 6.61(1H, d, J=7.9-8.2 Hz), 6.77-7.12(6H, m)								

Table D-126

## Example 126

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Et			Me			Me		
Reaction1								
Compound I-b3(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	1.720	1.270	1.07	38.00	14	nHc:EA =2:1	I-a126	2.110
Reaction2								
Compound I-a126(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.050	2.20	0.820	59.00	2	nHc:EA:MC =1:3:1	I-b126	2.000	
Reaction3								
Compound I-b126(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
1.950	0.290	27.00	2	EA:MeOH =10:1	1.350	18.09		
ESI-MS(M <sup>+</sup> +1):587								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.60, 0.79 and 0.91(6H, d, J=6.4-6.5Hz), 1.00 and 1.04(t, 3H, J=6.7-7.2Hz), 1.34 and 1.39(9H, s), 2.18-2.89(7H, m) 2.52 and 2.77(3H, s), 2.95 and 3.04(3H, s), 3.22 and 3.39(1H, dd, J=14.0-15.0, 7.9-7.6Hz),3.57 and 3.70(t, 1H, J=6.8, 6.9Hz), 4.59-4.73(2H, m),5.05 and 5.13(1H, d, J=10.6-10.7Hz), 5.13 and 5.31(1H, dd, J=9.0,7.3Hz), 6.45 and 6.62(1H, d, J=7.9 and 8.04Hz), 6.78-7.12(6H, m)								

T02121-6T00580

Table D-127

## Example 127

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
H			Me			Et		
Reaction1								
Compound I-b5 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.240	0.990	0.91	20.00	12	nHc:EA =1:1	I-a127	0.440
Reaction2								
Compound I-a127(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.420	0.76	0.035	5.00	12	nHc:EA =1:1	I-b127	0.370	
Reaction3								
Compound I-b127(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.350	0.050	15.00	3	MC:MeOH =20:1	0.100	18.26		
ESI-MS(M <sup>+</sup> +1):573								
1H-NMR(CDCl <sub>3</sub> ) : (two rotamers) δ 0.67, 0.81 and 0.91(6H, d, J=5.9-6.9Hz), 1.07 and 1.16(3H, t, J=6.8 and 6.1Hz), 1.33 and 1.38(9H, s), 2.24-2.49(2H, m), 2.58-2.75(1H, m), 2.78 and 3.05(3H, s), 2.83-3.03(1H, m), 3.15-3.30(1H, m), 3.37-3.44(1H, m), 3.55-3.65(1H, m), 3.75-3.90(1H, m), 4.55-4.76(2H, m), 4.85-5.06(2H, m), 6.43 and 6.61(1H, d, J=8.1-8.4Hz), 6.75-7.1(6H, m), 7.36 and 8.03(1H, brs)								

T02121 6T206860

Table D-128

## Example 128

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Me			Me			Et		
Reaction1								
Compound I-b5(g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.230	0.950	0.91	20.00	12	nHx:EA =1:1	I-a128	0.640
Reaction2								
Compound I-a128(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.610	1.10	0.051	3.00	12	nHx:EA =1:1	I-b128	0.560	
Reaction3								
Compound I-b128(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.540	0.080	23.00	1	MC:MeOH=20:1		0.200	18.85	
ESI-MS(M <sup>+</sup> +1):587								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.77, 0.83, 0.84 and 0.93(6H, d, J=6.4-6.8Hz), 1.12 and 1.18(3H, t, J=7.0-7.1Hz), 1.34 and 1.38(9H, s), 2.25(3H, s), 2.29-2.39(1H, m), 2.64-3.01(3H, m), 2.75 and 2.85(3H, s), 3.21-3.33(1H, m), 3.42-3.69(3H, m), 4.58-4.76(2H, m), 4.88-4.94 and 5.10-5.19(1H, m), 5.12(1H, dd, J=10.5, 2.6Hz), 6.50 and 6.61(1H, d, J=8.0Hz), 6.80-6.98(3H, m), 7.07-7.15(3H, m), 7.42 and 8.29(1H, t, J=6.0-6.4Hz)								

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FOI 2025-00000



Table D-129

## Example 129

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Et			Me			Et		
Reaction1								
Compound I-b5 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.370	1.010	0.92	25.00	12	nHx:EA =1:1	I-a129	0.970
Reaction2								
Compound I-a129(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.950	1.70	0.079	6.00	12	nHx:EA =1:1	I-b129	0.790	
Reaction3								
Compound I-b129(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.780	0.120	30.00	2	MC:MeOH =20:1		0.300	19.68	
ESI-MS(M <sup>+</sup> +1):601								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.76, 0.82, 0.83 and 0.92(6H, d, J=6.4-6.9Hz), 1.00-1.28(6H, m), 1.34 and 1.38(9H,s), 2.25-2.43(2H, m), 2.49-2.59(1H, m), 2.65-2.97(3H, m), 2.72 and 2.79(3H, s), 3.17-3.33(1H, m), 3.41-3.76(3H, m), 4.52-4.74(2H, m), 4.85-4.90 and 5.12-5.16(1H, m), 5.09(1H, dd J=10.7, 3.5Hz), 6.48 and 6.59(1H, d, J=8.0-8.4Hz), 6.80-6.98(3H, m), 7.08-7.17(3H, m), 7.38 and 8.32(1H, t, J=5.7Hz)								

Table D-130

## Example 130

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
H			Et			Et		
Reaction1								
Compound I-bl1 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.250	1.000	0.68	25.00	30	nHx:EA =1:1	I-a130	0.200
Reaction2								
Compound I-a130(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.200	0.36	0.400	4.00	12	nHx:EA =1:1	I-b130	0.100	
Reaction3								
Compound I-b130(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.100	0.015	5.00	1	MC:MeOH =25:1		0.016	18.41	
ESI-MS(M <sup>+</sup> +1):587								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) d 0.54, 0.81, 0.87 and 0.93(6H, d, J=6.0-6.8Hz), 1.12 and 1.19(6H, t, J=6.8-7.2Hz), 1.36 and 1.39(9H, s), 2.25-2.43(1H, m), 2.60-2.74(1H, m), 2.78-2.99(2H, m), 3.16-3.50(4H,m), 3.56-3.80(2H, m), 4.53-4.74(2H, m), 4.83-4.88 and 4.99-5.11(2H, m), 6.48 and 6.63(1H, d, J=7.9Hz), 6.80-6.85 and 6.96-7.18(6H, m), 7.46-7.49 and 7.58-								

T020201 67205250

Table D-131

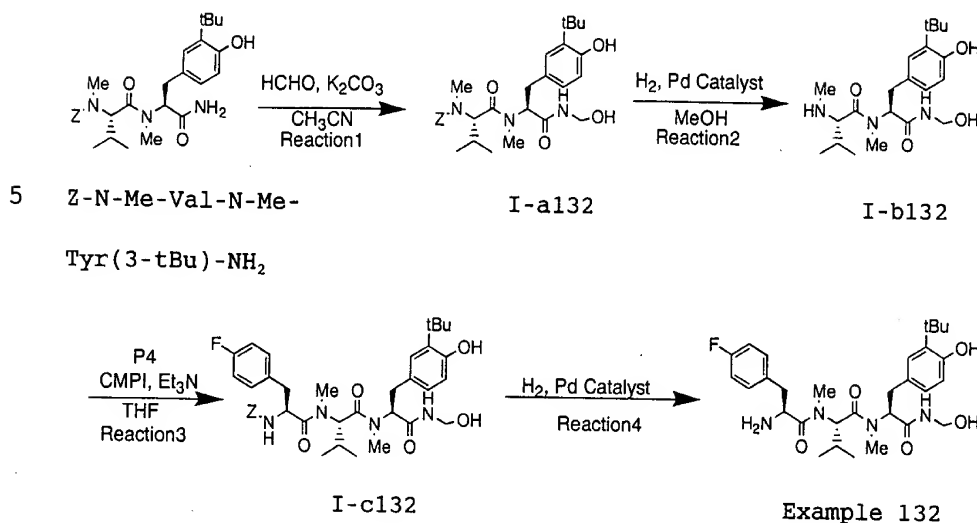
## Example 131

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31			R32			R33		
Me			Et			Et		
Reaction1								
Compound I-b11 (g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.340	1.000	0.68	25.00	30	nHx:EA =1:1	I-a131	0.170
Reaction2								
Compound I-a131(g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.170	0.31	0.014	4.00	12	nHx:EA =1:1	I-b131	0.080	
Reaction3								
Compound I-b131(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.080	0.012	4.00	1	MC:MeOH =25:1		0.040	18.97	
ESI-MS(M <sup>+</sup> +1):601								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 0.64(1H, d, J=6.4Hz), 0.85-0.97(7H, m), 1.10-1.19(4H, m), 1.33 and 1.37(9H, s), 2.25-2.43(1H, m), 2.29 and 2.31(3H, s), 2.67-2.86(3H, m), 3.12-3.65 and 3.74-3.81(6H, m), 4.52-4.72(2H, m), 4.87-4.92 and 5.09-5.19(2H, m), 6.45 and 6.59(1H, d, J=8.0 and 8.4Hz), 6.78(2/3H, dd, J=7.9, 1.5Hz), 6.90-6.98(7/3H, m), 7.04(2/3H, d, J=1.5Hz), 7.10-7.16(7/3H, m), 7.50 and 7.90(1H, t, J=6.3 and 6.0Hz)								

Scheme 5 shows the synthesis process of Example 132.

Scheme 5: Synthesis process of Example 132



The synthesis process in scheme 5 is explained below.

10    Reaction step 1)

To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> in CH<sub>3</sub>CN, 38% HCHO and K<sub>2</sub>CO<sub>3</sub> were added and stirred at room temperature. The reaction mixture was mixed with a saturated aqueous NH<sub>4</sub>Cl solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a132.

20

Reaction step 2)

To a solution of Compound I-a132 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room

temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b132.

5

Reaction step 3)

To a solution of Compound I-b132, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-cl32.

15

Reaction step 4)

To a solution of Compound I-cl32 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-132 shows Example conducted according to Scheme 5.

Table D-132

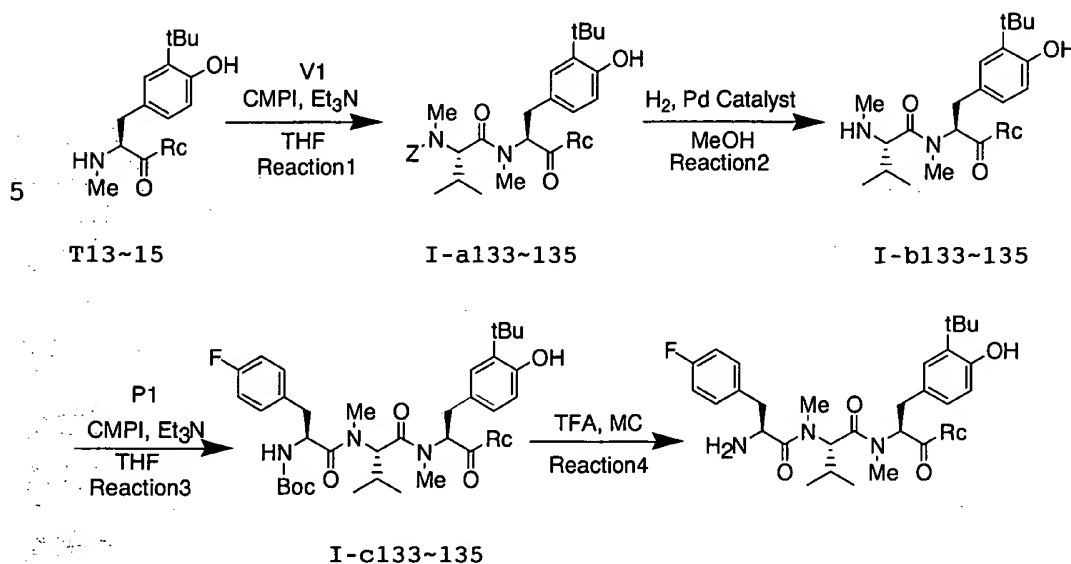
## Example 132

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH<sub>2</sub>OH

R31				R32		R33		
H				Me		Me		
Reaction1								
Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	HCHO (ml)	K <sub>2</sub> CO <sub>3</sub> (g)	CH <sub>3</sub> CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.000	3.00	1.100	71.00	2	nHc:EA:MC=1:3:1	I-a132	2.000	
Reaction2								
Compound I-a132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.950	0.290	50.00	1	EA:MeOH=7:1		I-b132	0.730	
Reaction3								
Compound I-b132(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	0.880	0.700	0.50	35.00	4	nHc:EA=1:4	I-c132	0.700
Reaction4								
Compound I-c132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	0.110	10.00	4	MC:MeOH=20:1		0.410	16.64	
ESI-MS(M <sup>+</sup> +1):559								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.49, 0.74, 0.78 and 0.91(6H, d, J=5.9-6.6Hz), 1.33 and 1.37(9H, s), 2.20-2.97(4H, m), 2.54, 2.81 and 3.00(6H, s), 3.16 and 3.35(1H, dd, J=13.7-15.1, 6.2-6.5Hz), 3.71 and 3.85(1H, dd, J=8.1-9.4, 4.5-5.0Hz), 4.64 and 4.69(2H, d, J=6.0-6.4Hz), 4.79 and 5.06(1H, d, J=10.2-10.6Hz), 5.00 and 5.36(1H, dd, J=9.2, 5.5Hz), 6.43 and 6.64(1H, d, J=7.8Hz), 6.71-7.12(6H, m)								

Scheme 6 shows the synthesis process of Examples 133-135.

Scheme 6: Synthesis process of Examples 133-135



10 Rc in the above Scheme indicates the substituent shown in Tables D-133 to D-135.

The synthesis process in scheme 6 is explained below.  
Reaction step 1)

15 To solutions of Compounds T13 to T15, Compound V1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

20 The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a133 to I-





dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

- 5            Tables D-133 to D-135 show Examples conducted according to Scheme 6.

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Table D-133

## Example 133

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-morpholine								
Reaction1								
Compound T13(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.490	0.720	0.50	20.00	20	nHx:EA = 1:1	I-a133	0.900
Reaction2								
Compound I-a133(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.900	0.100	20.00	20	MC:MeOH = 20:1		I-b133	0.600	
Reaction3								
Compound I-b133(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.450	0.530	0.40	20.00	20	nHx:EA = 1:1	I-c133	0.850
Reaction4								
Compound I-c133 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.850	3.00	10.00	4	MC:MeOH = 20:1		0.600	19.77	
ESI-MS(M <sup>+</sup> +1):599								
1H-NMR(CDC1 <sub>3</sub> ): (two rotamers) δ 0.78 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.24(3H, s), 2.48-2.56(1H, m), 2.79-2.87(5H, m), 3.02-3.09(1H, m), 3.40-3.74(10H, m), 5.01-5.05(1H, J=10.0 Hz), 5.79-5.84(1H,m), 6.39 and 6.41(1H,d, J=7.9Hz), 6.74-6.77(1H,m), 6.99-7.18(6H,m)								

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Table D-134

## Example 134

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-{[3-(tert-butyl)-4-hydroxyphenyl]methyl}-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-(methylsulfonyl) piperazine								
Reaction1								
Compound T14(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	0.790	1.100	0.84	20.00	20	nHx:EA = 1:1	I-a134	1.500
Reaction2								
Compound I-a134 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.500	0.300	20.00	20	M C:MeOH = 20:1		I-b134	0.900	
Reaction3								
Compound I-b134 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.520	0.430	0.38	15	2	nHx:EA = 1:1	I-c134	0.700
Reaction4								
Compound I-c134 (g)	TFA (ml)	M C (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	3.00	10.00	4	M C:MeOH = 20:1		0.350	19.94	
ESI-MS(M <sup>+</sup> +1):677								
1H-NMR(CDC <sub>13</sub> ): (two rotamers) δ 0.79 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.52-2.69(4H, m), 2.73(3H, s), 2.75-2.89(7H, m), 3.01-3.16(4H, m), 3.58-3.78(1H, m), 5.03 and 5.07(1H, d, J=10.6 Hz), 5.75-5.81(1H, m), 6.42 and 6.45(1H, d, J=7.9Hz), 6.76-6.80(1H, m), 6.99-7.18(6H, m)								

Table D-135

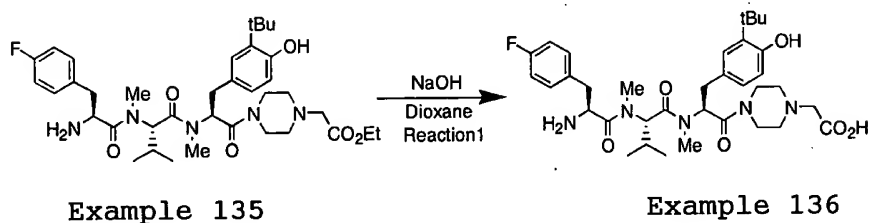
## Example 135

Ethyl 2-[4-((2S)-2-((2S)-2-((2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino)-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetate

R								
ethyl-2-piperazinylacetate								
Reaction1								
Compound T15 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.643	0.547	0.527	0.50	16.00	16	nHx:EA= 2:3	I-a135	0.827
Reaction2								
Compound I-a135 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.827	0.250	13.00	1	MC:MeOH =20:1		I-b135	0.645	
Reaction3								
Compound I-b135 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.645	0.458	0.413	0.40	12	16	nHx:EA= 2:3	I-c135	0.796
Reaction4								
Compound I-c135(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.796	2.00	5.00	1	MC:MeOH =30:1		0.430	17.1	
ESI-MS(M <sup>+</sup> +1):684								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.77 and 0.84(6H, d, J=6.4-6.8Hz), 1.26(3H, t, J=7.1Hz), 1.26(9H, s), 2.22-2.30(1H, m), 2.47-2.54(1H, m), 3.00-3.07(1H, m), 2.40, 2.81 and 3.18(6H, s), 3.54-3.73(5H, m), 4.18(2H, q, J=7.1Hz), 5.03(2H, d, J=10.4Hz), 5.85(1H, t, J=2.3Hz), 6.40(1H, d, J=7.9Hz), 6.72-6.75 (1H, dd, J=9.7, 1.9Hz), 7.00-7.26(5H, m)								

Scheme 7 shows the synthesis process of Example 136.

Scheme 7: Synthesis process of Example 136



Reaction step 1)

The compound obtained in Example 135 was added to a dioxane solution, mixed with a 2N-NaOH solution and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-136 shows Example conducted according to Scheme 7.

Table D-136

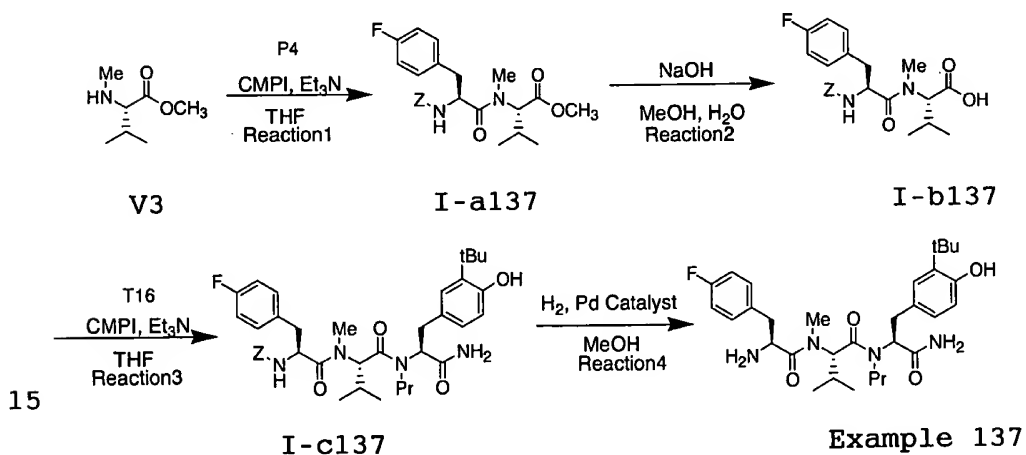
Example 136

2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetic acid

Reaction							
Compound of Example 135(g)	NaOH (g)	H <sub>2</sub> O (ml)	Dioxane (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.375	0.400	5.00	5.00	16	MC:MeOH=20:1	0.200	14.97
ESI-MS(M <sup>+</sup> +1):656							
<sup>1</sup> H-NMR(CD <sub>3</sub> OD): (two rotamers) δ 0.78 and 0.82(6H, d, J=6.1Hz), 1.27(9H, s), 2.12-2.29(1H, m), 2.74-3.12(8H, m), 3.61-3.82(4H, m), 2.48, 2.94, 3.25 and 3.55(6H, s), 4.50-4.56(1H, q, J=10.5Hz), 5.02(1H, d, J=10.5Hz), 5.73(1H, t, J=7.9Hz), 6.74-6.78(1H, dd, J=9.4, 2.2Hz), 7.00-7.27(6H, m)							

Scheme 8 shows the synthesis process of Example 137.

Scheme 8: Synthesis process of Example 137



The synthesis process in scheme 8 is explained below.

Reaction step 1)



[illegible]

To a solution of Compound 1-cl37 in methanol, Pd/C  
5 was added and stirred in a hydrogen atmosphere at room  
temperature. After filtering off the Pd/C, the filtrate  
was concentrated under reduced pressure; the thus obtained  
residue was purified by column chromatography (silica gel)  
to give the titled compound.

10



Table D-137

## Example 137

Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH<sub>2</sub>

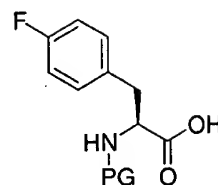
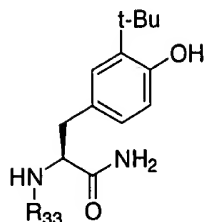
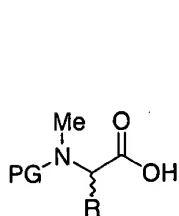
Reaction1								
Compound V3 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.146	3.000	2.410	2.20	28.00	12	nHx:EA=5:1	I-a137	1.877
Reaction2								
Compound I-a137(g)	NaOH (g)	H <sub>2</sub> O (ml)	MeOH (ml)	Reaction time (hr)	Product		Amount (g)	
1.870	0.646	8.00	40.00	8	I-b137		1.710	
Reaction3								
Compound I-b137(g)	Compound T10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.710	0.709	0.976	0.88	14.00	12	nHx:EA=3:2	I-c137	0.610
Reaction4								
Compound I-c137(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.080	16.00	1	MC:MeOH =25:1		0.128	22.7	
ESI-MS(M <sup>+</sup> ):557								
1H-NMR(CDCl <sub>3</sub> ): δ 0.66(3H, d, J=6.6Hz), 0.80(3H, d, J=6.5Hz), 0.84(3H, t, J=7.4Hz), 1.33(9H, s), 1.43-1.59(2H, m), 2.20-2.28(1H, m), 2.53(1H, dd, J=13.5, 9.1Hz), 2.60-2.75(2H, m), 2.95(1H, dd, J=13.8, 4.8Hz), 3.01(3H, s), 3.20(1H, dd, J=14.1, 6.2Hz), 3.32(1H, dd, J=13.6, 10.9Hz), 3.52-3.63(1H, m), 3.89-3.93(1H, m), 4.21-4.28(1H, m), 4.89(1H, d, J=10.6Hz), 5.48(1H, brs), 6.51(1H, d, J=7.9Hz), 6.73(1H, dd, J=7.9, 1.9Hz), 6.82(1H, brs), 6.99-7.10(3H, m), 7.11-7.16(2H, m)								

5

The processes of synthesizing Intermediates of Schemes 9-14 are shown below as Reference Examples. In addition, structural formulae of Intermediates of Examples 138-176 are shown in Tables C-3 and C-4.

Table C-3

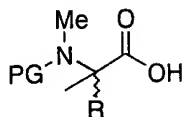
Intermediates of Examples 138-176



- |    |   |            |                 |
|----|---|------------|-----------------|
|    | I1: R=Et , I2: R=Et(D)  | T1: R33=H  | P1: PG=Z or Boc |
| 5  | I3: R=n-Pr, I4: R=n-Pr(D)   | T4: R33=Me | P4: PG=Z or Boc |
|    | I5: R=s-Bu (commercial), I6: R=s-Bu(D)                                    |            |                 |
|    | I7: R=i-Bu (commercial), I8: R=i-Bu(D)                                    |            |                 |
|    | I9: R=Allyl, I10: R=Allyl(L,D-mixture)                                    |            |                 |
|    | I11: R=neo-Pentyl, I12: R=neo-Pentyl(D)                                   |            |                 |
| 10 | I13: R=CH <sub>2</sub> CF <sub>3</sub> (L,D-mixture)                      |            |                 |
|    | I14: R=c-Hex, I15: R=c-Hex(D)   |            |                 |
|    | I16: R=CH <sub>2</sub> c-Hex, I17: R=CH <sub>2</sub> c-Hex(D)             |            |                 |
|    | I18: R=CH <sub>2</sub> Ph, I19: R=CH <sub>2</sub> Ph(D)                   |            |                 |
|    | I20: R=CH <sub>2</sub> Ph(4-F), I21: R=CH <sub>2</sub> Ph(4-F)(D)         |            |                 |
| 15 | I22: R=CH <sub>2</sub> Ph(4-Cl), I23: R=CH <sub>2</sub> Ph(4-Cl)(D)       |            |                 |
|    | I24: R=CH <sub>2</sub> Ph(4-OBn), I25: R=CH <sub>2</sub> Ph(4-OBn)(D)     |            |                 |
|    | I26: R=CH <sub>2</sub> (2-thienyl), I27: R=CH <sub>2</sub> (2-thienyl)(D) |            |                 |
|    | I28: R=CH <sub>2</sub> c-Pr   |            |                 |
|    | I38: R=tBu  |            |                 |
| 20 | I29: N-Me-Phg-OMe, I30: N-Me-D-Phg-OMe                                    |            |                 |

Table C-4

Intermediates of Examples 138-176 (continued)

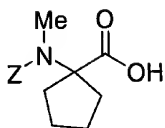


I31: R=CH<sub>2</sub>Ph, I32: R=CH<sub>2</sub>Ph(D)

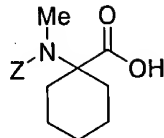
5 I33: R=i-Bu

I34: R=Et(D)

I35: R=i-Pr(D)



I36



I37

10

In Tables C-3 and C-4, "commercial" means that the compound is commercially available, "(D)" means a D-amino acid in stereochemistry and those which are not indicated as (D) are L-amino acids. PG in the Intermediate (I)

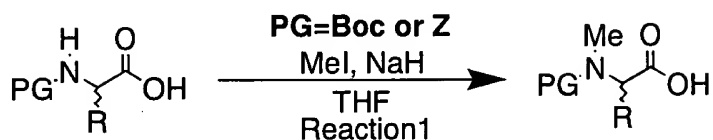
15 means Z or Boc.

Reference Example 21

Synthesis of Intermediates I1 to I28

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates I1 to I28



Z or Boc-Amino acid

I1-28

10 The synthesis process of Intermediates I1 to I28 is explained below.

Reaction step 1)

To solutions of Z- and Boc-protected amino acids in THF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixtures were mixed with  
15 water, adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column  
20 chromatography (silica gel) to give Compounds I1 to I28.

Results are shown in Tables E-10 to E-35.

Table E-10

Intermediates I1: Z-N-Me-Abu-OH

R						
Et						
Reaction						
Z-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	4.20	1.340	40.00	15	MC:MeOH =10:1	1.400

5 Table E-11

Intermediate I2: Boc-N-Me-D-Abu-OH

R						
Et:D						
Reaction						
Boc-(D)-Abu- OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.750	1.83	0.738	18.00	48	MC:MeOH =8:1	0.810

Table E-12

10 Intermediate I3: Z-N-Me-Nva-OH

R						
n-Pr						
Reaction						
Z-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	5.00	0.960	30.00	24	MC:MeOH =10:1	2.090

Table E-13

Intermediate I4: Boc-N-Me-D-Nva-OH

R						
n-Pr:D						
Reaction						
Boc-(D)-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.87	0.552	25.00	40	MC:MeOH =10:1	1.000

5 Table E-14

Intermediate I6: Boc-N-Me-D-Ile-OH

R						
s-Bu:D						
Reaction						
Boc-(D)-Ile-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.500	1.35	0.866	17.00	12	MC:MeOH =10:1	0.490

Table E-15

10 Intermediate I8: Boc-N-Me-D-Leu-OH

R						
i-Bu:D						
Reaction						
Boc-(D)-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.49	1.600	17.00	12	MC:MeOH =15:1	0.960

Table E-16

Intermediate I9:

(2S)-2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl						
Reaction						
(2S)-2-[(tert-butoxy)carbonylamino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.660	1.79	1.150	12.00	12	MC:MeOH =10:1	0.570

5

Table E-17

Intermediate I10:

2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl: D,L-mixture						
Reaction						
2-[(tert-butoxy)carbonyl - amino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.656	7.67	4.924	51.00	12	MC:MeOH =15:1	2.360

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Table E-18

Intermediate I11: BOC-N-Me-Leu( $\gamma$ -Me)-OH

R						
neo-Pent						
Reaction						
BOC-Leu( $\gamma$ -Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.930	4.86	3.120	40.00	48	MC:MeOH =10:1	1.500

5 Table E-19

Intermediate I12: BOC-N-Me-D-Leu( $\gamma$ -Me)-OH

R						
neo-Pent:D						
Reaction						
BOC-(D)-Leu( $\gamma$ -Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.50	1.630	20.00	24	MC:MeOH =10:1	1.110

Table E-20

10 Intermediate I13: 2-[N-(phenylmethoxy)carbonyl-methylamino]-4,4,4-trifluorobutanoic acid

R						
CH <sub>2</sub> CF <sub>3</sub> :L,D-mixture						
Reaction						
Z-2-amino-4,4,4-trifluorobutanoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.75	1.61	1.03	20.00	12	MC:MeOH =10:1	0.567



Table E-21

Intermediate I14: Boc-N-Me-Chg-OH

R						
c-Hex						
Reaction						
Boc-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.60	2.300	40.00	20	MC:MeOH =30:1	1.500

5 Table E-22

Intermediate I15: Boc-N-Me-D-Chg-OH

R						
c-Hex:D						
Reaction						
Boc-(D)-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.70	1.740	30.00	20	MC:MeOH =30:1	1.150

10 Table E-23

Intermediate I16: Boc-N-Me-Cha-OH

R						
CH <sub>2</sub> c-Hex						
Reaction						
Boc-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.40	1.100	23.00	18	MC:MeOH =10:1	1.300

Table E-24

Intermediate I17: Boc-N-Me-D-Cha-OH

R						
CH <sub>2</sub> c-Hex:D						
Reaction						
Boc-(D)-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.72	0.552	11.50	18	MC:MeOH =10:1	1.000

5 Table E-25

Intermediate I18: Boc-N-Me-Phe-OH

R						
CH <sub>2</sub> Ph						
Reaction						
Boc-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-26

10 Intermediate I19: Boc-N-Me-D-Phe-OH

R						
CH <sub>2</sub> Ph:D						
Reaction						
Boc-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.890	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-27

Intermediate I20: Boc-N-Me-Phe(4-F)-OH

R						
CH <sub>2</sub> Phe(4-F)						
Reaction						
Boc-Phe-(4-F)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
15.000	27.00	6.360	180.00	24	MC:MeOH =10:1	15.000

5 Table E-28

Intermediate I21: Boc-N-Me-D-Phe(4-F)-OH

R						
CH <sub>2</sub> Phe(4-F):D						
Reaction						
Boc-(D)-Phe(4-F)- OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.76	0.424	12.00	18	MC:MeOH =10:1	1.000

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FOI 221 61206260

Table E-29

Intermediate I22: Boc-N-Me-Phe(4-Cl)-OH

R						
CH <sub>2</sub> Ph(4-Cl)						
Reaction						
Boc-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.32	0.800	40.00	18	MC:MeOH =20:1	1.630

5 Table E-30

Intermediate I23: Boc-N-Me-D-Phe(4-Cl)-OH

R						
CH <sub>2</sub> Ph(4-Cl):D						
Reaction						
Boc-(D)-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.401	20.00	18	MC:MeOH =20:1	0.781

Table E-31

10 Intermediate I24: Boc-N-Me-Phe(4-OBn)-OH

R						
CH <sub>2</sub> Ph(4-OBn)						
Reaction						
Boc-Phe(4-OBn)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.500	3.35	0.808	50.00	36	MC:MeOH =20:1	2.590

[illegible]

5 Intermediate I26: Boc-N-Me-Ala( $\beta$ -2-thienyl)-OH

R						
CH <sub>2</sub> (2-Thienyl)						
Reaction						
Boc-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	0.916

Intermediate I27: Boc-N-Me-D-Ala( $\beta$ -2-thienyl)-OH

R						
CH <sub>2</sub> (2-Thienyl):D						
Reaction						
Boc-(D)-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	1.040

Table E-35

Intermediate I28: Z-N-Me-Ala( $\beta$ -c-Pr)-OH

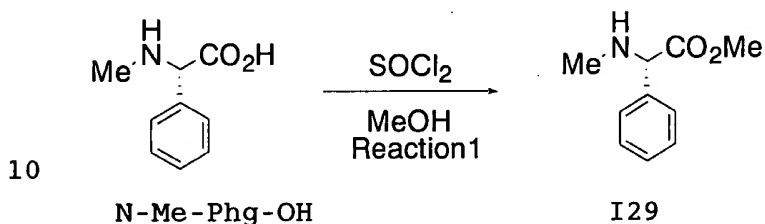
R						
CH <sub>2</sub> c-Propyl						
Reaction						
Z-N-Ala(beta-c-Pr)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.84	0.680	15.00	15	MC:MeOH =10:1	1.160

# 5 Reference Example 22

## Synthesis of Intermediate I29

The synthesis scheme is shown below.

## Synthesis scheme of Intermediate I29



The synthesis process of Intermediate I29 is explained below.

15

## Reaction step 1)

To a solution of N-Me-Phg-OH in methanol, SOCl<sub>2</sub> was slowly added dropwise under cooling and then stirred under reflux. The reaction mixture was concentrated under reduced pressure to give crude Compound I29.

20

Result is shown in Table E-36.

Table E-36

Intermediate I29: N-Me-Phg-OMe

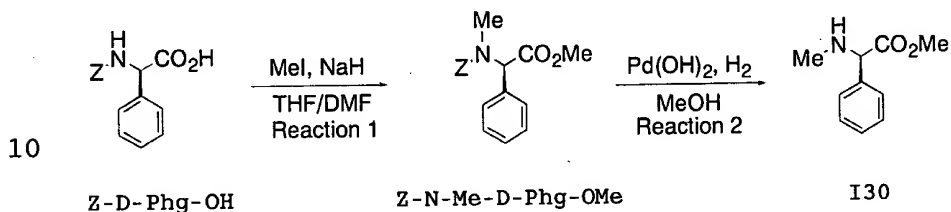
Reaction				
N-Me-Phg-OH (g)	SOCl <sub>2</sub> (ml)	MeOH (ml)	Reaction time (hr)	Amount (g)
2.000	1.32	20.00	3.00	2.000

5 Reference Example 23

Synthesis of Intermediate I30

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I30



The synthesis process of Intermediate I30 is explained below.

15 Reaction step 1)

To a solution of Z-D-Phg-OH and CH<sub>3</sub>I in THF and DMF, NaH was slowly added dropwise and then stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Z-N-Me-D-Phg-OMe.

20

# Reaction step 2)

To a solution of Z-N-Me-D-Phg-OMe in methanol, palladium hydroxide/carbon was added and stirred in a hydrogen atmosphere at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel), giving Compound I30.

Result is shown in Table E-37.

Table E-37

Intermediate I30: N-Me-D-Phg-OMe

R							
Ph :D							
Reaction1							
Z-N-Me-(D)-Phg-OH (g)	Methyl iodide (ml)	NaH (g)	THF/DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	3.49	0.842	20.00 (10.00/10.00)	16	nHx:EA=5:1	Z-N-Me-(D)-Phg-OMe	2.200
Reaction2							
Z-N-Me-(D)-Phg-OMe(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Column sol.	Amount (g)	
2.200	0.330	40.00	12		nHx:EA=5:1	1.240	

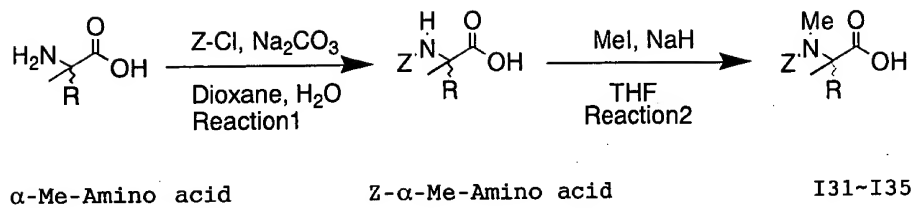
## Reference Example 24

### Synthesis of Intermediates I31-I35

The synthesis scheme is shown below.

### Synthesis scheme of Intermediates I31-I35





The synthesis process of Intermediates I31 to I35 is  
 5 explained below.

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Reaction step 1)

To solutions of  $\alpha$ -Me-amino acids and  $\text{Na}_2\text{CO}_3$  in dioxane and water, Z-Cl was slowly added dropwise under cooling while stirring. The reaction mixtures were mixed with  
5 water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel), giving Z- $\alpha$ -Me-amino acids.

10

Reaction step 2)

T solutions of the Z- $\alpha$ -Me-Amino acid and  $\text{CH}_3\text{I}$  in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl,  
15 extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to giving Compounds I31 to I35.

20

Results are shown in Tables E-38 to E-42.

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Table E-38

Intermediate I31: Z-N-Me- $\alpha$ -Me-Phe-OH

R								
CH <sub>2</sub> Ph								
Reaction1								
alpha-Me-Phe-OH (g)	Z-Cl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-Phe-OH	0.890
Reaction2								
Z-alpha-Me-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.890	1.40	0.340	28.00	15	MC:MeOH =10:1		1.180	

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Table E-39

Intermediate I32: Z-N-Me- $\alpha$ -Me-D-Phe-OH

R								
CH <sub>2</sub> Ph:D								
Reaction1								
alpha-Me-(D)-Phe-OH (g)	Z-Cl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-(D)-Phe-OH	0.810
Reaction2								
Z-alpha-Me-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.810	1.40	0.340	28.00	15	MC:MeOH =10:1		1.050	

5

Table E-40

Intermediate I33: Z-N-Me- $\alpha$ -Me-Leu-OH

R								
i-Bu								
Reaction1								
alpha-Me-Leu-OH (g)	Z-Cl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.970	2.10	2.140	30.00	20.00	24	MC:MeOH =10:1	Z-alpha-Me-Leu-OH	2.000
Reaction2								
Z-alpha-Me-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
2.000	4.40	2.000	35.00	12	MC:MeOH =10:1		1.780	

10

Table E-41

Intermediate I34: Z-N-Me- $\alpha$ -Me-D-Abu-OH

R								
CH <sub>2</sub> CH <sub>3</sub> :D								
Reaction1								
alpha-Me-(D)- Abu-OH (g)	Z-Cl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	THF (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.36	0.450	10.00	2.00	3	MC:MeOH =10:1	Z-alpha-Me- (D)-Et-OH	0.177
Reaction2								
Z-alpha-Me- (D)-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.750	0.42	0.190	10.00	12	MC:MeOH=10:1		0.152	

5

Table E-42

Intermediate I35: Z-N-Me- $\alpha$ -Me-D-Val-OH

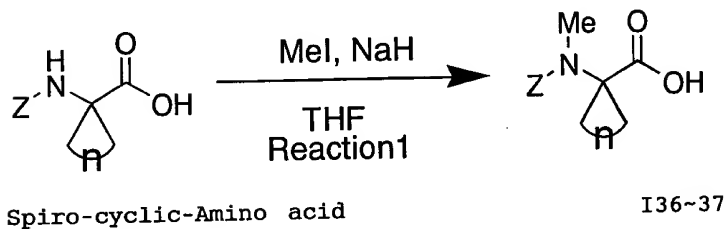
R								
i-Pr:D								
Reaction1								
alpha-Me-(D)- Val-OH (g)	Z-Cl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.31	1.454	4.00	4.00	12	MC:MeOH =15:1	Z-alpha-Me- (D)-Val-OH	0.170
Reaction2								
Z-alpha-Me-(D)- Val-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.170	0.40	0.128	3.00	12	MC:MeOH=10:1		0.170	

Reference Example 25

Synthesis of Intermediate I36, I37

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates I36 and I37



10 The synthesis process of Intermediates I36 and I37 is explained below.

Reaction step 1)

To solutions of a spiro-cyclic-amino acids and  $\text{CH}_3\text{I}$  in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I36 and I37.

Results are shown in Tables E-43 and E-44.

Table E-43

Intermediate I36:

1-[N-

methyl(phenylmethoxy)carbonylamino]cyclopentanecarboxylic

5 acid

Reaction						
Z-1-amino-1-cyclopentanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.79	0.912	26.00	18	MC:MeOH =20:1	1.730

Table E-44

Intermediate I37:

1-[N-

10 methyl(phenylmethoxy)carbonylamino]cyclohexanecarboxylic

acid

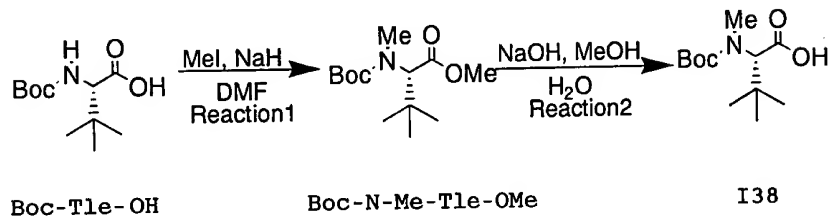
Reaction						
Z-1-amino-1-cyclohexanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	7.19	1.730	80.00	18	MC:MeOH =20:1	4.190

Reference Example 26

Synthesis of Intermediate I38

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate I38



0000219.121001  
0000219.121001  
The synthesis process of Intermediate I38 is  
10 explained below.

Reaction step 1)

To a solution of Boc-Tle-OH in DMF, NaH and MeI were added under cooling and stirred at room temperature. The  
15 reaction mixture was mixed with 1N HCl, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give Boc-N-Me-Tle-OMe.

20 Reaction step 2)

To a solution of Boc-N-Me-Tle-OMe in methanol and water, NaOH was added and stirred at room temperature. The reaction mixture was adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated  
25 brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the



thus obtained residue was purified by column chromatography (silica gel), giving Intermediate I38.

Result is shown in Table E-45.

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Table E-45

Intermediate I38: Boc-N-Me-Tle-OH

Reaction1						
Boc-Tle-OH (g)	Methyl iodide (ml)	NaH (g)	DMF (ml)	Reaction time (hr)	Product	Amount (g)
1.000	2.70	0.865	18.00	16	Boc-N-Me-Tle-OMe	1.180
Reaction2						
Boc-N-Me-Tle-OMe (g)	NaOH (g)	MeOH (ml)	H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.180	0.550	10.00	2.00	22	MC:MeOH=10:1	0.900

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09690249-16491  
TOTAL: 6720990

The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The  
5 filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b.

Reaction step 2-b)

10 To solutions of Compounds I-a in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica  
15 gel) to give Compounds I-b.

Reaction step 3)

To solutions of Compounds I-b138 to I-b165, Compound P1 or P4 and CMPI in THF, TEA was added under cooling and  
20 stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by  
25 column chromatography (silica gel) to give Compounds I-c138 to I-c165.

Reaction step 4-a)

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To solutions of Compounds I-c in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous NaHCO<sub>3</sub> solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

10

Reaction step 4-b)

To solutions of Compounds I-c in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Compounds which were synthesized in Examples according to Scheme 9 are shown in Tables D-138 to D-165. In the tables "A" indicated after the Example number means "less polar isomer" and "B" means "more polar isomer". For example, Compound of Example 150A is "less polar isomer" of Phe(4-F)-N-Me-Ala( $\beta$ -CF<sub>3</sub>)-N-Me-Tyr(3-tBu)-NH<sub>2</sub> and Compound of Example 150B is "more polar isomer" of Phe(4-F)-N-Me-Ala( $\beta$ -CF<sub>3</sub>)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>.

Table D-138

## Example 138

Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
Et								
Reaction1								
Compound T4 (g)	Compound I1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.960	0.980	0.90	30.00	12	nHx:EA=1:2	I-a138	1.420
Reaction2-b								
Compound I-a138(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.400	0.430	28.00	2	MC:MeOH=15:1	I-b138		0.950	
Reaction3								
Compound I-b138(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.890	0.860	0.780	0.70	5.00	72	nHx:EA=1:1	I-c138	0.720
Reaction4-a								
Compound I-c138(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.720	1.80	9.00	3	MC:MeOH=15:1	0.420		17.07	
ESI-MS(M <sup>+</sup> +1):515								
1H-NMR(CD <sub>3</sub> OD):(two rotamers) δ 0.55 and 0.88(3H, t, J=7.2-7.6Hz), 1.39 and 1.44(9H, s), 1.56-1.85(2H, m), 2.23, 2.62, 2.91 and 2.98(6H, s), 2.56-3.01(4H, m), 3.26(1H, dt, J=3.0-4.7, 13.9-15.4Hz), 3.78 and 3.97(1H, dd, J=8.4, 5.1Hz), 5.28 and 5.55(1H, dd, J=7.8-11.6, 4.8-6.0Hz), 6.59 and 6.74(1H, d, J=8.0Hz), 6.69-7.30(6H, m)								

Table D-139

## Example 139

Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
Et:D								
Reaction1								
Compound T4 (g)	Compound I2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.800	0.950	0.85	60.00	12	nHx:EA =1:2	I-a139	1.100
Reaction2-a								
Compound I-a139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.100	4.90	26.00	1	MC:MeOH =8:1	I-b139		0.770	
Reaction3								
Compound I-b139(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.750	0.670	0.60	44.00	72	nHx:EA =1:2	I-c139	1.310
Reaction4-a								
Compound I-c139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
1.300	4.20	21.00	2	MC:MeOH= 15:1	0.620		19.96	
ESI-MS(M <sup>+</sup> +1):515								
1H-NMR(CD <sub>3</sub> OD): δ 0.48(3H, t, J=7.5Hz), 1.36(9H, s), 1.38-1.43(2H, m), 2.59 and 2.87(3H, s), 2.73(1H, dd, J=13.2, 7.5 Hz), 2.81-2.92(2H, m), 3.02 and 3.14(3H, s), 3.37(1H, dd, J=15.0, 6.1Hz), 3.93(1H, t, J=6.8-7.1Hz), 4.82(1H, t, J=7.7Hz), 5.34(1H, brs), 5.50(1H, dd, J=11.3, 5.9Hz), 6.42(1H, brs), 6.57(1H, d, J=7.8Hz), 6.88(1H, dd, J=7.7, 2.0Hz), 6.96(2H, t, J=8.6Hz), 7.08(1H, d, J=2.3Hz), 7.13(2H, m)								

Table D-140

## Example 140

Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
n-Pr								
Reaction1								
Compound T4 (g)	Compound I3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.830	0.800	0.847	0.84	30.00	24	nHx:EA =1:2	I-a140	1.372
Reaction2-b								
Compound I-a140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.372	0.200	80.00	2	MC:MeOH =10:1	I-b140		0.895	
Reaction3								
Compound I-b140(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c140	0.744
Reaction4-b								
Compound I-c140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.727	0.200	50.00	2	MC:MeOH =10:1	0.450		19.05	
ESI-MS(M <sup>+</sup> +1):529								
1H-NMR(CDCl <sub>3</sub> +CD <sub>3</sub> OD): (two rotamers) δ 0.20 and 0.70-1.20(3H, m), 0.65 and 0.75(3H, t, J=6.9Hz), 1.50-1.70(1H, m), 1.33 and 1.38(9H, s), 2.30 and 2.69(3H, s), 2.47 and 2.70(2H, m), 2.72(3H,s), 2.80 and 2.92(2H, m), 3.65 and 3.85(1H,m), 4.83(1H, m), 5.84(1H, m), 6.48(1H, d, J=9.69Hz), 6.70-6.82(1H, m), 6.90-7.20(5H, m)								



Table D-141

## Example 141

Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
n-Pr:D								
Reaction1								
Compound T4 (g)	Compound I4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.650	0.547	0.665	0.70	20.00	16	nHx:EA =1:2	I-a141	0.670
Reaction2-a								
Compound I-a141(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
0.670	1.50	10.00	2	MC:MeOH =10:1	I-b141		0.500	
Reaction3								
Compound I-b141(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.490	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c141	0.680
Reaction4-b								
Compound I-c141(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.680	0.100	20.00	2	MC:MeOH =10:1	0.358		22.27	
ESI-MS(M <sup>+</sup> +1):529								
1H-NMR(CDCl <sub>3</sub> +CD <sub>3</sub> OD): (two rotamers) δ 0.65-0.90(2H, m), 0.75(3H, t, J=6.9Hz), 1.20-1.50(2H, m), 1.37 and 1.39(9H, s), 2.75(2H, brs), 2.85 and 2.87(3H,s), 2.80(1H, m), 3.00 and 3.02(3H, s), 3.45(1H, m), 3.95(1H, t, J=7.2Hz), 4.91(1H, t, J=7.5Hz), 5.40(2H, m, brs), 6.40(1H, brs), 6.60(1H, d, J=9.3Hz), 6.37(1H, d, 9.3Hz), 6.90-7.18(5H, m)								

Table D-142

## Example 142

Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
s-Bu								
Reaction1								
Compound T4 (g)	Compound I5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.750	1.000	0.910	0.83	19.00	12	nHx:EA= 2:3	I-a142	1.350
Reaction2-b								
Compound I-a142 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.300	0.190	50.00	2	MC:MeOH =20:1	I-b142		0.920	
Reaction3								
Compound I-b142 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	0.830	0.750	0.67	25.00	12	nHx:EA=2:3	I-c142	1.170
Reaction4-a								
Compound I-c142 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
1.150	2.75	13.00	3	MC:MeOH =20:1	0.710		19.710	
ESI-MS(M <sup>+</sup> +1):543								
1H-NMR(CDCl <sub>3</sub> + CD <sub>3</sub> OD):(two rotamers) δ 0.38, 0.81, 0.85 and 0.88(6H, d, J=6.0-6.5Hz), 0.93-1.02(1H, m), 1.18-1.29(1H, m), 1.34 and 1.39(9H, s), 1.97-2.11(1H, m), 2.38-2.93(3H, m), 2.50, 2.86, 2.95 and 3.00(6H, s), 3.11-3.18(1H, m), 3.69 and 3.84(1H, dd, J=8.0-8.9, 4.0-5.5Hz), 4.91-4.96 and 5.02-5.14(4/3H, m), 5.45(2/3H, dd, J=10.2, 5.7Hz), 6.48(2/3H, d, J=7.9Hz), 6.65-6.71(1H, m), 6.91-7.12(16/3H, m)								

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Table D-143

## Example 143

Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
s-Bu:D								
Reaction1								
Compound T4 (g)	Compound I6 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.420	0.490	0.510	0.46	10.00	12	nHx:EA =2:3	I-a143	0.330
Reaction2-a								
Compound I-a143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
0.310	0.94	4.70	3	MC:MeOH = 10:1	I-b143		0.240	
Reaction3								
Compound I-b143 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.240	0.220	0.200	0.18	6.00	12	nHx:EA =2:3	I-c143	0.340
Reaction4-a								
Compound I-c143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.330	1.20	6.00	4	MC:MeOH = 10:1	0.140		23.200	
ESI-MS(M <sup>+</sup> +1):543								
1H-NMR(CDCI <sub>3</sub> ): δ 0.27(3H, d, J=6.8Hz), 0.67-0.80(4H, m), 0.88-0.97(1H, m), 1.36(9H, s), 1.74-1.85(1H, m), 2.71(1H, dd, J=13.9, 7.2Hz), 2.84-3.00(2H, m), 2.96(3H, s), 3.12(3H, s), 3.35(1H, dd, J=14.6, 5.2Hz), 3.96(1H, t, J=7.0Hz), 4.79(1H, d, J=11.0Hz), 5.46(1H, dd, J=11.5, 5.4Hz), 5.50(1H, brs), 6.35(1H, brs), 6.58(1H, d, J=8.0Hz), 6.90-7.05(4H, m), 7.12-7.16(2H, m)								

Table D-144

## Example 144

Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
i-Bu								
Reaction1								
Compound T4 (g)	Compound I7 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.747	1.000	0.910	0.83	19.00	12	nHx:EA=2:3	I-a144	1.320
Reaction2-b								
Compound I-a144 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.300	0.190	50.00	2	MC:MeOH =20:1		I-b144	0.940	
Reaction3								
Compound I-b144 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.940	0.850	0.760	0.69	25.00	12	nHx:EA =2:3	I-c144	1.230
Reaction4-a								
Compound I-c144 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.210	2.90	14.50	3	MC:MeOH =20:1		0.750	19.380	
ESI-MS(M <sup>+</sup> +1):543								
1H-NMR(CD <sub>3</sub> OD):(two rotamers) δ 0.66, 0.73, 0.94 and 0.96(6H, d, J=6.0-6.6Hz),1.37 and 1.40(9H, s), 1.40-1.52(2H, m), 1.55-1.68(1H, m), 2.26 and 2.65(3H, s), 2.53-2.69(1H, m), 2.69-3.00(1H, m),2.86 and 3.00(3H, s), 3.09-3.29(1H, m),3.72-3.78 and 3.90-3.94(1H, m), 4.56-4.64(1H, m),4.94-5.06(1H, m), 5.39-5.52(1H, m), 6.55-6.78(2H, m), 6.94-7.30(5H, m)								

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Table D-145

## Example 145

Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
i-Bu:D								
Reaction1								
Compound T4 (g)	Compound I8 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.810	0.960	1.000	0.91	25.00	12	nHx:EA=2:3	I-a145	1.450
Reaction2-a								
Compound I-a145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.430	4.60	23.00	3	MC:MeOH =5:1		I-b145	1.140	
Reaction3								
Compound I-b145 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.140	1.010	0.910	0.83	25.00	12	nHx:EA=2:3	I-c145	0.940
Reaction4-a								
Compound I-c145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.920	2.20	11.00	3	MC:MeOH =5:1		0.60	21.40	
ESI-MS(M <sup>+</sup> +1):543								
1H-NMR(CDCI <sub>3</sub> ): δ 0.72(3H, d, J=4.3Hz), 0.73(3H, d, J=4.1Hz), 0.81-0.92(2H, m), 1.24-1.30(1H, m), 1.36(9H, s), 2.73-2.90(3H, m), 2.84(3H, s), 2.99(3H, s), 3.30(1H, dd, J=14.6, 5.6Hz), 3.96(1H, t, J=7.2Hz), 5.02(1H, dd, J=9.9, 4.9Hz), 5.44(1H, dd, J=10.9, 5.6Hz), 5.63(1H, brs), 6.38(1H, brs), 6.57(1H, d, J=8.4Hz), 6.85(1H, dd, J=7.8, 1.9Hz), 6.91-7.01(3H, m), 7.09-7.13(2H, m)								

TABLE D-145

Table D-146

## Example 146

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide

R								
Allyl								
Reaction1								
Compound T4 (g)	Compound I9 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.573	0.630	0.700	0.64	14.00	12	nHx:EA=2:3	I-a146	0.900
Reaction2-a								
Compound I-a146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.870	2.90	14.0	3	MC:MeOH=10:1		I-b146	0.660	
Reaction3								
Compound I-b146 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.620	0.560	0.51	17.00	12	nHx:EA =2:3	I-c146	0.570
Reaction4-a								
Compound I-c146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.550	1.35	5.40	3	MC:MeOH=10:1		0.36	17.750	
ESI-MS(M <sup>+</sup> +1):527								
1H-NMR(CDCI <sub>3</sub> ): (two rotamers) δ 0.97-1.04(1/2H, m), 1.34 and 1.36(9H, s), 2.12-2.24(1/2H, m), 2.32-2.75(2H, m), 2.34 and 2.66(3H, s), 2.84-2.99(2H, m), 2.97(3H, s), 3.07-3.18(1H, m), 3.62-3.66 and 3.83-3.87(1H, m), 4.80-5.09(3H, m), 5.25-5.33 and 5.63-5.76(1H, m), 5.35-5.46(1H, m), 5.39(1H, brs), 6.06(0.5H, brs), 6.41 and 6.58(1H, d, J=8.2 and 8.0Hz), 6.74 and 6.83(1H, dd, J=7.9, 1.9Hz), 6.92-7.00(2H, m), 7.03-7.14(3H, m), 7.36(1/2H, brs)								

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Table D-147

Example 147

(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide

R								
Allyl:D								
Reaction1								
Compound T4 (g)	Compound I10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.180	1.300	1.440	1.30	30.00	12	nHx:EA =1:1	I-a147	0.340
Reaction2-a								
Compound I-a147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.330	1.10	5.00	3	MC:MeOH=7:1		I-b147	0.270	
Reaction3								
Compound I-b147 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.220	0.30	6.00	12	nHx:EA =2:3	I-c147	0.370
Reaction4-a								
Compound I-c147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	1.30	5.00	3	MC:MeOH=7:1		0.24	20.320	
ESI-MS(M <sup>+</sup> +1):527								
1H-NMR(CDCl <sub>3</sub> ): δ 1.35(9H, s), 1.99-2.16(2H, m), 2.64-2.72(1H, m), 2.79-2.89(2H, m), 2.87(3H, s), 2.97(3H, s), 3.31(1H, d, J=15.3, 5.9Hz), 3.90(1H, t, J=7.0Hz), 4.87-4.93(2H, m), 5.01(1H, dd, J=9.0, 6.7Hz), 5.16-5.29(1H, m), 5.44(1H, dd, J=10.5, 6.0Hz), 5.50(1H, brs), 6.37(1H, brs), 6.57(1H, d, J=7.8Hz), 6.85(1H, dd, J=7.9, 1.9Hz), 6.92-6.98(2H, m), 7.02(1H, d, J=2.2Hz), 7.09-7.13(2H, m)								

Table D-148

## Example 148

Phe(4-F)-N-Me-Leu( $\gamma$ -Me)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
neo-Pent								
Reaction1								
Compound T4 (g)	Compound I11 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.780	0.770	0.35	25.00	48	nHx:EA =1:2	I-a148	0.850
Reaction2-a								
Compound I-a148(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.800	2.50	12.50	4	MC:MeOH=9:1		I-b148	0.600	
Reaction3								
Compound I-b148(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.580	0.470	0.42	30.00	12	nHx:EA:MC =1:2:1	I-c148	0.950
Reaction4-b								
Compound I-c148(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.950	0.140	13.00	3	MC:MeOH=20:1		0.58	20.96	
ESI-MS(M <sup>+</sup> +1):557								
1H-NMR(CD <sub>3</sub> OD):(two rotamers) δ 0.71 and 0.99(9H, s), 1.43 and 1.46(9H, s), 1.28-1.40(2H, m), 2.43, 2.81, 2.97 and 3.07(6H, s), 2.23-3.04(4H, m), 3.25-3.28(1H, m), 3.79(2/3H, m), 3.92(1/3H, dd, J=9.8, 4.6Hz), 5.58 and 5.53(1H, dd, J=6.9-8.2, 4.8-6.9Hz), 6.61 and 6.80(1H, d, J=8.2Hz), 6.74-7.37(6H, m)								

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Table D-149

Example 149

Phe(4-F)-N-Me-D-Leu( $\gamma$ -Me)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
neoPent:D								
Reaction1								
Compound T4 (g)	Compound I12 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.990	0.980	0.90	30.00	12	nHx:EA=1:2	I-a149	1.250
Reaction2-a								
Compound I-a149(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.250	3.90	19.50	3	MC:MeOH=20:1		I-b149	0.99	
Reaction3								
Compound I-b149(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.970	0.780	0.71	50.00	5	nHx:EA=1:2	I-c149	1.500
Reaction4-b								
Compound I-c149(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.500	0.230	20.00	2	MC:MeOH=20:1		0.83	22.63	
ESI-MS(M <sup>+</sup> +1):557								
1H-NMR(CD <sub>3</sub> OD):(two rotamer) δ 0.62 and 0.84(9H, s), 0.88 and 1.35(2H, s), 1.40(9H, s), 2.45 and 2.82(3H, s), 2.84-2.95(3H m), 3.04 and 3.10(3H, s), 3.23(1H, dd, J=14.7, 4.9Hz), 4.65(1H, dd, J=8.0, 2.3Hz), 5.28(1H, m), 5.45(1H, dd, J=11.8, 5.1Hz), 6.63(1H, d, J=7.9Hz), 6.88(1H, dd, J=8.0, 2.3Hz), 7.01(2H, m), 7.10(1H, d, J=2.3Hz), 7.25(2H, dd, J=8.5, 5.4Hz)								

Table D-150A

Example 150A(less polar)

Phe(4-F)-N-Me-Ala( $\beta$ -CF<sub>3</sub>)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> CF <sub>3</sub> :L,D-mixture								
Reaction1								
Compound T4(g)	Compound I13(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.560	0.560	0.51	20.00	5.000	nHx:EA=1:1	I-a150	0.980
Reaction2-b								
Compound I-a150(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.980	0.500	20.00	2	MC:MeOH =15:1		I-b150A	0.360(less polar)	
						I-b150B	0.280(more polar)	
Reaction3								
Compound I-b150A(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.360	0.310	0.270	0.27	15.00	12	nHx:EA=1:1	I-c150A	0.32
Reaction4-b								
Compound I-c150A(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.310	0.150	10.00	2	EA:MeOH =15:1		0.200	18.66	
ESI-MS(M <sup>+</sup> +1): 569								
1H-NMR(CD3OD):(two rotamers) δ 1.38 and 1.41(9H, s), 2.20, 2.56, 2.91, and 2.99(6H, s), 2.38-3.03(4H, m), 3.25 and 3.31(1H, d, J=4.8Hz), 3.72(1H, t, J=7.2Hz), 4.73(1H, brs), 5.53 and 5.57(1H, d, J=4.6Hz), 5.80(1H, q, J=4.4Hz), 6.55-6.79(2H, m), 7.00-7.15(3H, m), 7.25-7.30(2H, m)								

Phe(4-F)-N-Me-Ala( $\beta$ -CF<sub>3</sub>)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> CF <sub>3</sub> -L,D-mixture								
Reaction3								
Compound I-b150B(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.200	0.20	15.00	12.00	nHx:EA =1:1	I-c150B	0.300
Reaction4-b								
Compound I-c150B(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.300	0.150	10.00	2	EA:MeOH =20:1	0.170	21.51		
ESI-MS(M <sup>+</sup> +1): 569								
1H-NMR(CD <sub>3</sub> OD):(two rotamers) δ 1.40(9H, s), 2.19-2.40(2H, m), 2.73 and 2.76(1H, d, J=7.0Hz), 2.89(3H, s), 2.92-2.96(1H, m), 2.98(3H, s), 3.21 and 3.24(1H, d, J=6.1Hz), 4.03(1H, t, J=7.2Hz), 4.52-4.61(1H, m), 5.36(1H, q, J=5.5Hz), 5.61(1H, t, J=7.0Hz), 6.67(1H, d, J=8.0Hz), 6.89(1H, dd, J=7.9, 2.4Hz), 7.01-7.10(3H, m), 7.24-7.29(2H, m)								

Table D-151

## Example 151

Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
c-Hex								
Reaction1								
Compound T4 (g)	Compound I14(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.290	1.500	2.650	1.45	30.00	20	nHx:EA=1:1	I-a151	0.700
Reaction2-a								
Compound I-a151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.700	4.00	20.00	4	MC:MeOH =20:1		I-b151	0.400	
Reaction3								
Compound I-b151(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.380	0.760	0.41	20.00	20	nHx:EA=1:1	I-c151	0.500
Reaction4-a								
Compound I-c151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.500	4.00	20.00	4	MC:MeOH =20:1		0.400	20.140	
ESI-MS(M <sup>+</sup> +1): 569								
1H-NMR(CDCI <sub>3</sub> ): (two rotamers) δ 0.72-1.68(10 H, m), 1.35 and 1.40(9H, s), 1.82-2.10(1H, m), 2.30-2.65(1H, m), 2.52(3H,s), 2.70-2.90(1H, m), 2.75(3H, s), 2.75-2.90(1H, m), 3.05-3.40(3H, m), 3.60-3.85(1H, m), 5.05-5.20(2H, m), 6.35-6.75(2H, m), 6.75-7.20(5H, m)								

Table D-152

## Example 152

Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
c-Hex:D								
Reaction1								
Compound T4 (g)	Compound I15(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.620	1.520	0.69	20.00	20	nHx:EA=1:1	I-a152	0.540
Reaction2-a								
Compound I-a152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.540	3.00	15.00	4	MC:MeOH =20:1		I-b152	0.250	
Reaction3								
Compound I-b152(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.240	0.470	0.26	15.00	20	nHx:EA=1:1	I-c152	0.350
Reaction4-a								
Compound I-c152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	3.00	10.00	4	MC:MeOH =20:1		0.27	22.040	
ESI-MS(M <sup>+</sup> +1): 569								
1H-NMR(CDC13): (two rotamers) δ 0.65-1.70(11H, m), 1.38(9H, s), 2.15-2.35(1H, m), 2.25(3H, s), 2.75-3.05(1H, m), 2.95(3H, s), 3.10-3.25(3H, m), 5.20-5.27(2H, m), 5.55-5.65(1H, m), 6.15-6.25(2H, m), 6.54 and 6.57(2H, d, J=8.4 Hz), 6.75-6.95(1H, m), 7.05-7.15(2H, m)								

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Table D-153

## Example 153

Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> c-Hex								
Reaction1								
Compound T4 (g)	Compound I16 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.950	1.300	1.150	1.10	38.00	15	nHx:EA=1:1	I-a153	1.600
Reaction2-a								
Compound I-a153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.600	4.80	24.00	3	MC:MeOH =20:1		I-b153	0.840	
Reaction3								
Compound I-b153 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.840	0.680	0.620	0.60	20.00	15	nHx:EA=1:1	I-c153	1.100
Reaction4-a								
Compound I-c153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.100	2.40	12.00	3	MC:MeOH =30:1		0.50	21.154	
ESI-MS(M <sup>+</sup> +1): 583								
1H-NMR(CDC1 <sub>3</sub> ): (two rotamers) δ 0.09-1.88(13H, m), 1.35 and 1.26(9H, s), 2.32-2.80(2H, m), 2.46 and 2.74(3H, s), 2.83-3.27(3H, m), 2.99 and 3.03(3H, s), 3.59-3.73 and 3.81-3.95(1H, m), 4.62-4.74 and 5.11-5.25(1H, m), 5.27-5.59(2H, m), 6.08(1/2H, brs), 6.44 and 6.63(1H, d, J=7.9-8.3Hz), 6.77 and 6.87(1H, dd, J=7.2-7.5 1.8-1.9Hz), 6.92-7.20(5H, m), 7.59(1/2H, brs)								

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Table D-154

## Example 154

Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> c-Hex:D								
Reaction1								
Compound T4 (g)	Compound I17 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	1.000	0.900	0.80	29.00	15	nHx:EA=1:1	I-a154	1.200
Reaction2-a								
Compound I-a154(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.200	3.60	18.00	3	MC:MeOH =20:1		I-b154	0.740	
Reaction3								
Compound I-b154(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.740	0.600	0.540	0.50	17.00	15	nHx:EA=1:1	I-c154	0.900
Reaction4-a								
Compound I-c154 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	2.00	10.00	3	MC:MeOH =30:1		0.24	25.144	
ESI-MS(M <sup>+</sup> +1): 583								
1H-NMR(CDCl <sub>3</sub> ): δ 0.62-1.37(13H, m), 1.37(9H, m), 2.67-3.10(7H, m), 2.88(3H, s), 2.97(3H, s), 3.30 and 3.35(1H, d, J=3.3-3.4Hz), 3.95(1H, t, J=6.9Hz), 5.04 and 5.08(1H, d, J=4.2-4.5Hz), 5.43 and 5.47(1H, d, J=5.4-5.8Hz), 5.52(1H, brs), 6.37(1H, brs), 6.58(1H, d, J=7.9Hz), 6.79-7.09(4H, m), 7.11(1H, d, J=5.2Hz), 7.14(1H, d, J=5.4Hz)								

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**Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH<sub>2</sub>**

R								
CH <sub>2</sub> Ph								
Reaction1								
Compound T4 (g)	Compound I18 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	1.000	1.230	0.89	20.00	20	nHx:EA =1:1	I-a155	1.390
Reaction2-b								
Compound I-a155(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.390	0.300	20.00	20	MC:MeOH =20:1		I-b155	0.840	
Reaction3								
Compound I-b155(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	15.00	20	nHx:EA =1:1	I-c155	0.997
Reaction4-a								
Compound I-c155(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.997	3.00	10.00	4	MC:MeOH =20:1		0.68	19.710	
ESI-MS(M <sup>+</sup> +1): 577								
1H-NMR(CDCl <sub>3</sub> ):(two rotamers) δ 1.40 and 1.42(9H, s), 2.54(3H, s), 2.61-3.04(5H, m), 3.15-3.39(4H, m), 3.67-3.85(1H, m), 5.32-5.72(2H, m), 6.57-6.72(1H, m), 6.98-7.29(10H, m)								



Table D-156

## Example 156

Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Ph:D								
Reaction1								
Compound T4 (g)	Compound I19 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.800	1.230	0.89	20.00	20	nHx:EA=1:1	I-a156	1.140
Reaction2-a								
Compound I-a156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.140	3.00	10.00	4	MC:MeOH =20:1		I-b156	0.990	
Reaction3								
Compound I-b156(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	20.00	20	nHx:EA=1:1	I-c156	0.960
Reaction4-a								
Compound I-c156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.960	3.00	10.00	4	MC:MeOH =20:1		0.73	21.960	
ESI-MS(M <sup>+</sup> +1): 577								
1H-NMR(CDCI <sub>3</sub> ): δ 1.42(9H, s), 2.47-2.65(4H, m), 2.97-3.25(2H, m), 3.04(3H,s), 3.15(3H, s), 3.32-3.51(3H, m), 4.01-4.15(1H, m), 6.75-6.80(1H, m), 6.82-7.45(1H, m)								

T0221" 5T205360

Table D-157

## Example 157

Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Phe(4-F)								
Reaction1								
Compound T4 (g)	Compound I20 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.960	1.370	1.180	1.10	38.00	15	nHx:EA=1:2	I-a157	1.880
Reaction2-a								
Compound I-a157 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.880	5.40	27.00	3	MC:MeOH =20:1		I-b157	1.220	
Reaction3								
Compound I-b157(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.220	0.780	0.710	0.60	23.00	18	nHx:EA=1:2	I-c157	1.550
Reaction4-a								
Compound I-c157 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.550	3.30	16.00	3	MC:MeOH =20:1		0.73	21.035	
ESI-MS(M <sup>+</sup> +1): 595								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 1.28 and 1.35(9H, s), 2.30-3.25(12H, m), 2.38 and 2.56(3H, s), 2.86 and 2.99(3H, s), 3.49-3.72(1H, m), 4.84-5.17(1H, m), 5.18-5.41(2H, m), 5.51-5.78(1H, m), 6.38 and 6.43(1H, d, J=8.3Hz), 6.60-7.23(10H, m)								

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Table D-158

## Example 158

Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Phe(4-F):D								
Reaction1								
Compound T4 (g)	Compound I21 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.000	0.850	0.80	27.00	18	nHx:EA=1:2	I-a158	1.120
Reaction2-a								
Compound I-a158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.120	3.30	16.50	3	MC:MeOH =20:1		I-b158	0.880	
Reaction3								
Compound I-b158 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.880	0.560	0.500	0.50	16.00	15	nHx:EA=1:2	I-c158	0.900
Reaction4-a								
Compound I-c158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	2.00	10.00	3	MC:MeOH =20:1		0.30	23.049	
ESI-MS(M <sup>+</sup> +1): 595								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) d 1.34 and 1.37(9H, s), 2.38-2.51(1H, m), 2.53-2.82(5H, m), 2.86(3H, s), 2.88(3H, s), 3.04-3.15(1H, m), 3.21 and 3.26(1H, d, J=6.4-6.3), 3.78-3.95(1H, m), 5.26-5.38(1H, m), 5.38-5.52(1H, m), 5.62(1H, brs), 6.27(1H, brs), 6.79(1H, d, J=8.1Hz), 6.78(1H, d, J=8.7Hz), 6.83-7.22(9H, m)								

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Table D-159

## Example 159

Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Ph(4-Cl)								
Reaction1								
Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.080	1.630	1.330	0.91	20.00	16	nHx:EA=1:1	I-a159	2.000
Reaction2-a								
Compound I-a159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
2.000	5.60	25.00	1	MC:MeOH =20:1		I-b159	1.13	
Reaction3								
Compound I-b159 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.861	0.777	0.53	20.00	3	nHx:EA=1:1	I-c159	0.908
Reaction4-a								
Compound I-c159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.908	1.96	10.00	3	MC:MeOH =20:1		0.625	21.59	
ESI-MS(M <sup>+</sup> +1):612								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) d 1.28 and 1.35(9H,s), 2.38 and 2.55(3H, s), 2.40-3.32(6H, m), 2.85 and 3.0(3H, s), 3.56 and 3.72(1H, t, J = 8.8Hz), 4.92(2/5H, m), 5.20-5.50(5/2H, m), 5.60 and 5.78(3/5H, brs), 6.35-7.40(25/2H, m)								

Table D-160

## Example 160

Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Ph(4-Cl):D								
Reaction1								
Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.519	0.781	0.639	0.44	10.00	16	nHx:EA=1:1	I-a160	0.947
Reaction2-a								
Compound I-a160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.947	5.60	15.00	1	MC:MeOH =20:1		I-b160	0.624	
Reaction3								
Compound I-b160 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.476	0.430	0.30	15.00	3	nHx:EA=1:1	I-c160	0.46
Reaction4-a								
Compound I-c160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.460	1.00	5.00	3	MC:MeOH =20:1		0.300	19.53	
ESI-MS(M <sup>+</sup> +1):612								
1H-NMR(CDCl <sub>3</sub> ): d 1.35(9H,s), 1.30-2.96(5H, m), 2.88(3H, s), 2.89(3H, s), 3.03-3.35(1H, m), 3.83(3/4H, m), 5.29(2H, s), 5.43(6/4H, m), 6.20(3/4H, brs), 6.52(1H, d, J=8.8Hz), 6.78(1H, d, J=8.8Hz), 6.90-7.32(10H, m)								

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Table D-161

## Example 161

Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Ph(4-OH)								
Reaction1								
Compound T4 (g)	Compound I24 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	2.600	1.730	1.09	30.00	3	nHx:EA=1:1	I-a161	2.610
Reaction2-a								
Compound I-a161(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
2.610	6.47	33.00	3	MC:MeOH =20:1		I-b161	1.300	
Reaction3								
Compound I-b161 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.200	0.964	0.70	30.00	3	nHx:EA=1:1	I-c161	1.880
Reaction4-b								
Compound I-c161(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.880	0.282	40.00	3	MC:MeOH =20:1		0.500	17.94	
ESI-MS(M <sup>+</sup> +1):593								
1H-NMR(CD <sub>3</sub> OD): (two rotamers) d 1.41 and 1.42(9H,s), 2.32 and 2.39(3H, s), 2.90 and 3.07(3H, s), 2.59-3.50(7H, m), 3.72 and 3.85(1/2H, m), 5.05 and 5.30(1/2H, m), 5.60(1H, m), 6.50-7.43(11H, m)								

Table D-162

## Example 162

Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Ph(4-OH):D								
Reaction1								
Compound T4 (g)	Compound I25 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	2.000	1.220	0.77	30.00	3	nHx:EA=1:1	I-a162	1.550
Reaction2-b								
Compound I-a162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.550	0.233	20.00	12	MC:MeOH =20:1		I-b162	0.977	
Reaction3								
Compound I-b162 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.977	1.080	0.871	0.64	20.00	3	nHx:EA=1:1	I-c162	1.330
Reaction4-b								
Compound I-c162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.330	0.200	30.00	3	MC:MeOH =20:1		0.500	18.54	
ESI-MS(M <sup>+</sup> +1):593								
1H-NMR(CD <sub>3</sub> OD): δ 1.45(9H,s), 2.42-2.75(4H, m), 3.02(3H, s), 2.34-3.15(2H, m), 3.32(1/5H, dd, J =7.6, 8.8Hz), 4.03(4/5H, t, J=8.8Hz), 5.42-5.65(2H, m), 6.65-7.25(12H, m)								

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Table D-163

## Example 163

Phe(4-F)-N-Me-Ala( $\beta$ -2-thienyl)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> (2-Thienyl)								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.670	0.916	0.820	0.56	20.00	16	nHx:EA=1:1	I-a163	1.280
Reaction2-a								
Compound I-a163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.280	3.80	19.00	3	MC:MeOH =20:1		I-b163	0.513	
Reaction3								
Compound I-b163 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.418	0.379	0.30	20.00	3	nHx:EA=1:1	I-c163	0.587
Reaction4-a								
Compound I-c163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.587	1.32	10.00	3	MC:MeOH =20:1		0.35	23.7	
ESI-MS(M <sup>+</sup> +1):583								
1H-NMR(CDCl <sub>3</sub> + CD <sub>3</sub> OD): (two rotamers) δ 1.30 and 1.35(9H,s), 1.80(1/3H, m), 2.25, 2.58 and 2.88, 3.0(6H, s), 2.0-3.25(5H, m), 3.35(2/3H, m), 3.60(1H, m), 4.90(1/3H, m), 5.27(2/3H, m), 5.37-5.64(1H, m), 6.40-6.72(2H, m), 6.72-7.20(8H, m)								

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Table D-164

## Example 164

Phe(4-F)-N-Me-D-Ala( $\beta$ -2-thienyl)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> (2-Thienyl):D								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.040	0.930	0.64	20.00	16	nHx:EA=1:1	I-a164	1.430
Reaction2-a								
Compound I-a164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.430	4.43	25.00	3	MC:MeOH =20:1		I-b164	0.500	
Reaction3								
Compound I-b164 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.400	0.360	0.28	20.00	3	nHx:EA=1:1	I-c164	0.857
Reaction4-a								
Compound I-c164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.857	1.92	15.00	3	MC:MeOH =20:1		0.33	21.7	
ESI-MS(M <sup>+</sup> +1):583								
1H-NMR(CDCl <sub>3</sub> ): δ 1.35(9H,s), 2.17-3.20(7H, m), 2.91(3H, s), 2.95(3H, s), 3.28(1/2H, dd, J=15.8, 7.9Hz), 3.85(1/2H, t, J=7.9Hz), 5.35 and 5.45(2H, m), 5.65(1H, brs), 6.28(2/3H, brs), 6.48-7.30(28/3H, m)								

Table D-165

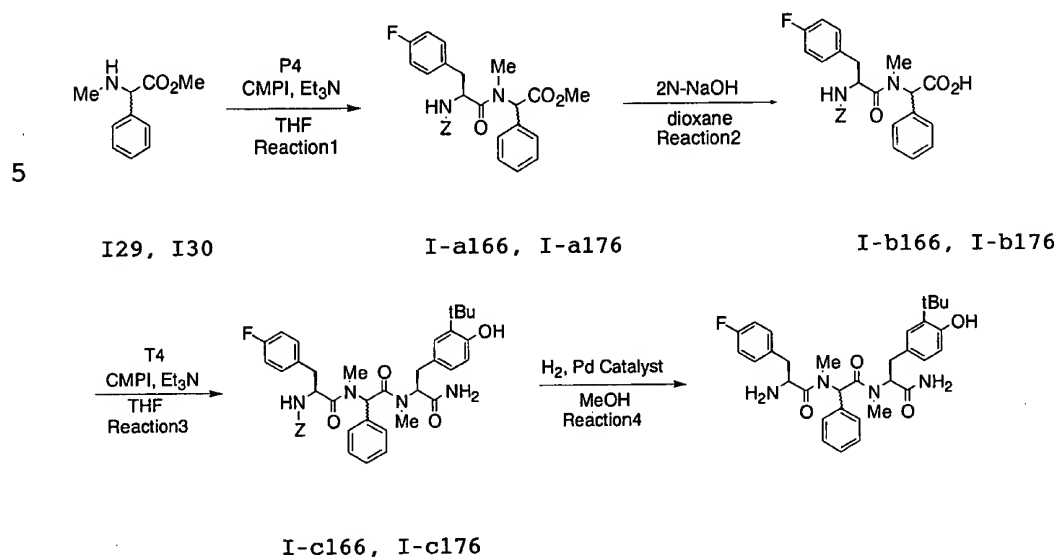
## Example 165

Phe(4-F)-N-Me-Ala( $\beta$ -c-Pr)-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> c-Pr								
Reaction1								
Compound T4 (g)	Compound I28 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.820	1.100	1.000	0.90	33.00	17	nHx:EA=1:1	I-a165	1.260
Reaction2-b								
Compound I-a165 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.260	0.120	24.00	3	MC:MeOH =30:1		I-b165	0.600	
Reaction3								
Compound I-b165 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.540	0.490	0.50	16.00	18	nHx:EA=1:1	I-c165	0.590
Reaction4-a								
Compound I-c165 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.590	1.40	7.00	3	MC:MeOH =30:1		0.300	18.61	
ESI-MS(M <sup>+</sup> +1): 541								
1H-NMR(CD <sub>3</sub> OD): (two rotamers) δ 0.85-0.78(5H, m), 1.39-1.91(2H, m), 1.47 and 1.49(9H, s), 2.34 and 2.69(3H, s), 2.49-3.38(4H, m), 2.98 and 3.03(3H, s), 3.75-3.48(1H, m), 5.06-5.15 and 5.49-5.67(2H, m), 6.65-6.88(2H, m), 7.04-7.43(5H, m)								

Scheme 10 shows the synthesis process of Examples 166 and 176.

Scheme 10: Synthesis process of Examples 166 and 176



The synthesis process in scheme 10 is explained below.

#### 10 Reaction step 1)

To solutions of Compound P4, Compounds I29 and I30 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a166 and I-a176.

20

#### Reaction step 2)

To solutions of Compounds I-a166 and I-a176 in

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dioxane, 2N NaOH was added and stirred at room temperature. The reaction mixtures were adjusted to pH 3 to 4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b166 and I-b176.

10 Reaction step 3)

To solutions of Compounds I-b166 and I-b176, Compound T4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c166 and I-c176.

20

Reaction step 4)

To solutions of Compounds I-c166 and I-c176 in methanol, Pd(OH)<sub>2</sub> was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd(OH)<sub>2</sub>, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Examples conducted according to Scheme 10 are shown in Tables D-166 and D-176.

[illegible]

Table D-166

## Example 166

Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
Compound I29 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	1.000	1.170	1.22	30.00	3	nHx:EA =1:1	I-a166	1.070

Reaction2						
Compound I-a166(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.070	2.50	20.00	3	MC:MeOH =20:1	I-b166	1.030

Reaction3								
Compound I-b166 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.030	0.504	0.668	0.42	20.00	3	nHx:EA =1:1	I-c166	0.595

Reaction4						
Compound I-c166(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.595	0.100	10.00	3	MC:MeOH =20:1	0.480	20.00

ESI-MS(M<sup>+</sup>+1):563

1H-NMR(CD<sub>3</sub>OD): (two rotamers) δ 1.40 and 1.49(9H,s), 2.75 and 2.90(3H, s), 2.95 and 3.15(3H, s), 2.53-3.50(5H, m) 4.12(1H, m), 4.74 and 5.32(1H, m), 6.40-7.58(15H, m)

Table D-176

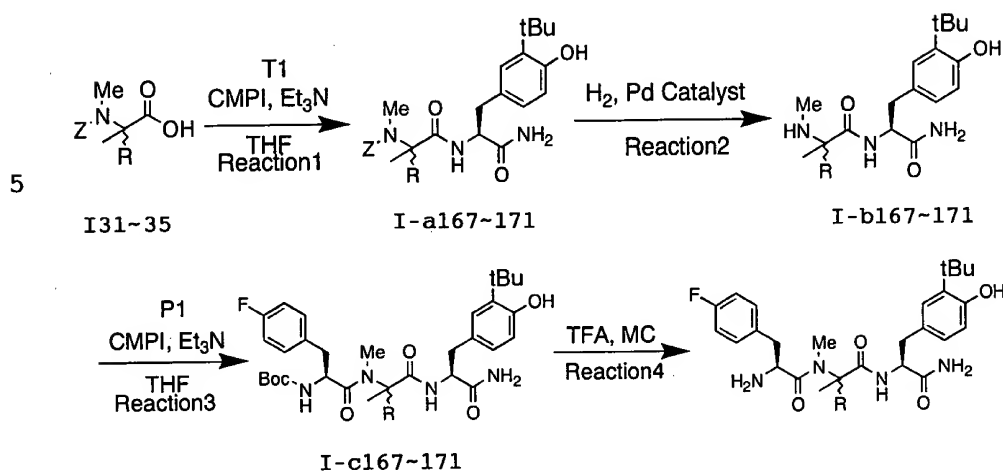
## Example 176

Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
Compound I30 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.646	2.160	2.300	1.45	20.00	3	nHx:EA =1:1	I-a176	1.030
Reaction2								
Compound I-a176(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.030	2.40	20.00	3	MC:MeOH =20:1		I-b176	0.540	
Reaction3								
Compound I-b176 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.540	0.268	0.355	0.22	10.00	3	nHx:EA =1:1	I-c176	0.450
Reaction4								
Compound I-c176(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.450	0.070	10.00	3	MC:MeOH =20:1		0.270	20.98	
ESI-MS(M <sup>+</sup> +1):563								
1H-NMR(CD <sub>3</sub> OD): δ 1.46(9H,s), 2.50(3H, s), 2.82(3H, s), 2.72-3.13(3H, m), 3.402H, m), 4.20(1H, m), 5.48(1H, dd, J=13.2, 6.2Hz), 6.25(1H, brs), 6.35(2H, d, J=8.8Hz), 6.75(1H, d, J=8.8Hz), 6.90(1H, dd, J=8.8, 1.7Hz), 7.05-7.45(8H, m)								

Scheme 11 shows the synthesis process of Examples 167-171.

Scheme 11: Synthesis scheme of Examples 167-171



The synthesis process in scheme 11 is explained below.

10 Reaction step 1)

To solutions of Compound T1, Compounds I31 to I35 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a167 to I-a171.

20

Reaction step 2)

To solutions of Compounds I-a167 to I-a171 in methanol, Pd/C was added and stirred in a hydrogen



atmosphere at room temperature. After filtering off the  
Pd/C, the filtrates were concentrated under reduced  
pressure; the thus obtained residues were purified by  
column chromatography (silica gel) to give Compounds I-b167  
5 to I-b171.

Reaction step 3)

To solutions of Compounds I-b167 to I-b171, Compound  
P1 and CMPI in THF, TEA was added under cooling and stirred  
10 at room temperature. The reaction mixtures were mixed with  
water, extracted with ethyl acetate, washed with saturated  
brine, dried over anhydrous magnesium sulfate and filtered.  
The filtrates were concentrated under reduced pressure; the  
thus obtained residues were purified by column  
15 chromatography (silica gel) to give Compounds I-c167 to I-  
c171.

Reaction step 4)

To solutions of Compounds I-c167 to I-c171 in  
20 dichloromethane, TFA was added under cooling and stirred at  
room temperature. The reaction mixtures were concentrated  
under reduced pressure, neutralized by the addition of a  
saturated  $\text{NaHCO}_3$  aqueous solution, extracted with ethyl  
acetate, dried over anhydrous magnesium sulfate and  
25 filtered. The filtrates were concentrated under reduced  
pressure; the thus obtained residues were purified by  
column chromatography (silica gel) to give the titled  
compounds.

Examples conducted according to Scheme 11 are shown  
in Tables D-167 to D-171.

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Total 6720880

Table D-167

## Example 167

Phe(4-F)-N-Me- $\alpha$ -Me-Phe-Tyr(3-tBu)-NH<sub>2</sub>

R								
CH <sub>2</sub> Phe								
Reaction1								
Compound T1 (g)	Compound I31 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.570	1.180	0.900	0.80	24.00	5	nHx:EA =1:2	I-a167	0.360
Reaction2								
Compound I-a167 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.360	0.040	6.00	3		I-b167		0.260	
Reaction3								
Compound I-b167 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.260	0.420	0.780	0.40	6.30	120	nHx:EA =1:2	I-c167	0.060
Reaction4								
Compound I-c167 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.060	0.20	0.70	3	MC:MeOH =20:1		0.01	21.813	
ESI-MS(M <sup>+</sup> +1): 577								
1H-NMR(CDCl <sub>3</sub> ): δ 1.30(3H, s), 1.34(9H, s), 2.37-2.62(3H, m), 2.51(3H, s), 3.07(1H, d, J=14.5Hz), 3.24-3.41(2H, m), 3.73(1H, t, J=8.3Hz), 4.48-4.57(1H, m), 5.37-5.58(2H, m), 6.50(1H, d, J=9.0Hz), 6.75(1H, d, J=9.3Hz), 6.77(1H, s), 6.97-7.37(9H, m)								

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Table D-168

## Example 168

Phe(4-F)-N-Me- $\alpha$ -Me-Phe-Tyr(3-tBu)-NH<sub>2</sub>:Diastereomeric mixture

R								
CH <sub>2</sub> Phe:D								
Reaction1								
Compound T1 (g)	Compound I32 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.390	0.820	0.640	0.60	16.00	5	nHx:EA =1:2	I-a168	0.670
Reaction2								
Compound I-a168 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.670	0.060	12.00	3		I-b168		0.500	
Reaction3								
Compound I-b168 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.810	1.400	1.20	12.00	120	nHx:EA =2:1	I-c168	0.210
Reaction4								
Compound I-c168 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.210	0.53	2.60	3	MC:MeOH =20:1		0.070	20.15/20.93	
ESI-MS(M <sup>+</sup> +1): 577								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 1.12-1.41(3H, m), 1.35(9H, s), 1.98 and 2.40(3H, s), 2.36(1H, s), 2.46-2.78(2H, m), 2.82-3.28(4H, m), 3.42-3.83(2H, m), 4.52-4.72(1H, m), 5.38-5.56(1H, m), 5.98-6.22(1H, m), 6.61-6.28(2H, m), 6.35-7.38(10H, m)								

Table D-169

## Example 169

Phe(4-F)-N-Me- $\alpha$ -Me-Leu-Tyr(3-tBu)-NH<sub>2</sub>

R								
i-Bu								
Reaction1								
Compound T1 (g)	Compound I33 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.560	1.770	2.310	1.68	60.00	12	nHx:EA:MC = 1:1.5:1	I-a169	2.390
Reaction2								
Compound I-a169(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
2.390	0.360	80.00	12		I-b169		1.490	
Reaction3								
Compound I-b169(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.490	1.230	1.510	1.10	78.00	12	nHx:EA=1:2	I-c169	0.910
Reaction4-a								
Compound I-c169(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.850	1.30	1.30	4	MC:MeOH =25:1		0.130	21.50	
ESI-MS(M <sup>+</sup> +1):543								
1H-NMR(CD <sub>3</sub> OD): δ 0.79(6H, t, J=7.0Hz), 1.27(3H, s), 1.46(9H, s), 1.51-1.79(3H, m), 2.54-2.67(2H, m), 2.76(3H, s), 3.04(1H, dd, J=14.3, 5.6Hz), 3.21(1H, dd, J=14.0, 6.8Hz), 3.81(1H, t, J=6.5-7.1Hz), 4.56(1H, dd, J=14.1, 6.4Hz), 5.39(1H, brs), 5.78(1H, brs), 6.61(1H, d, J=7.8Hz), 6.93-7.14(6H, m), 7.45(1H, brs)								

Table D-170

## Example 170

Phe(4-F)-N-Me- $\alpha$ -Me-D-Abu-Tyr(3-tBu)-NH<sub>2</sub>

R								
Et:D								
Reaction1								
Compound T1(g)	Compound I34(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.147	0.150	0.220	0.16	3.00	12	nHx:EA =1:1	I-a170	0.251
Reaction2								
Compound I-a170(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.250	0.150	5.00	3		I-b170		0.151	
Reaction3								
Compound I-b170(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.150	0.18	0.160	0.12	3.00	16	nHx:EA =1:1	I-c170	0.145
Reaction4								
Compound I-c170(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.140	0.60	3.00	2.5	EA:MeOH =20:1		0.075	19.5	
ESI-MS(M <sup>+</sup> +1):515								
1H-NMR(CDCl <sub>3</sub> ): δ 0.57(3H, t, J=7.6Hz), 1.21(3H, s), 1.37(9H, s), 1.63-1.82(2H, m), 1.70-1.92(2H, m), 2.59-2.71(2H, m), 2.72(3H, s), 3.03-3.21(2H, m), 3.84(1H, t, J=7.0Hz), 4.60(1H, q, J=6.0Hz), 5.51(1H, brs), 5.84(1H, d, J=7.3 Hz), 6.62(1H, d, J=8.0Hz), 6.91-7.03(5H, m), 7.09-7.14(2H, m), 7.54(1H, s)								

Table D-171

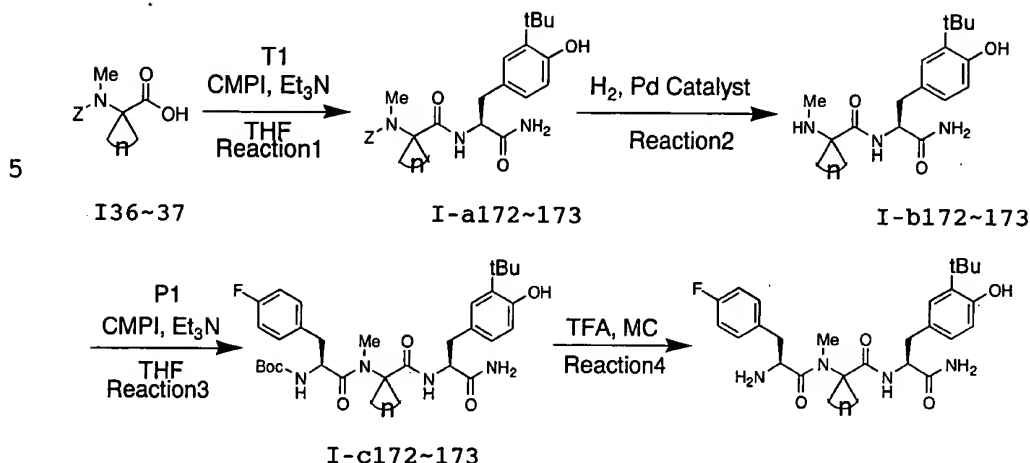
## Example 171

Phe(4-F)-N-Me- $\alpha$ -Me-D-Val-Tyr(3-tBu)-NH<sub>2</sub>

R								
i-Pr:D								
Reaction1								
Compound T1 (g)	Compound 135 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.144	0.170	0.150	0.17	3.6	12	nHx:EA=3:2	l-a171	0.120
Reaction2								
Compound l-a171(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.120	0.020	5.00	1.5		I-b171		0.080	
Reaction3								
Compound l-b171(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.080	0.190	0.170	0.12	2.00	30	nHx:EA=2:3	l-c171	0.050
Reaction4								
Compound l-c171(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.050	0.36	1.00	3	MC:MeOH =7:1		0.02	20.40	
ESI-MS(M <sup>+</sup> +1):529								
1H-NMR(CDCl <sub>3</sub> ): δ 0.69(3H, d, J=6.7Hz), 0.85(3H, d, J=6.7Hz), 1.16(3H, s), 1.36(9H, s), 1.76-1.92(1H, m), 2.27-2.44(1H, m), 2.52-2.70(2H, m), 2.82(3H, s), 3.03-3.24(2H, m), 4.54-4.62(1H, m), 5.47(1H, brs), 5.76(1H, d, J=7.5Hz), 6.60(1H, d, J=8.1Hz), 6.87-7.06(4H, m), 7.09-7.16(2H, m), 7.37(1H, brs)								

Scheme 12 shows the synthesis process of Examples 172 and 173.

Scheme 12: Synthesis scheme of Examples 172 and 173



The synthesis process in scheme 12 is explained below.

10 Reaction step 1)

To solutions of Compound T1, Compounds I36 and I37 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated  
15 brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a172 and I-173.

20

Reaction step 2)

To solutions of Compounds I-a172 and I-a173 in methanol, Pd(OH)<sub>2</sub> was added and stirred in a hydrogen



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atmosphere at room temperature. After filtering off the  
Pd(OH)<sub>2</sub>, the filtrates were concentrated under reduced  
pressure; the thus obtained residues were purified by  
column chromatography (silica gel) to give Compounds I-b172  
5 and I-b173.

Reaction step 3)

To solutions of Compounds I-b172 and I-b173, Compound  
P1 and CMPI in THF, TEA was added under cooling and stirred  
10 at room temperature. The reaction mixtures were mixed with  
water, extracted with ethyl acetate, washed with saturated  
brine, dried over anhydrous magnesium sulfate and filtered.  
The filtrates were concentrated under reduced pressure; the  
thus obtained residues were purified by column  
15 chromatography (silica gel) to give Compounds I-c172 and  
I-c173.

(Reaction step 4)

To solutions of Compounds I-c172 and I-c173 in  
20 dichloromethane, TFA was added under cooling and stirred at  
room temperature. The reaction mixtures were concentrated  
under reduced pressure, neutralized by the addition of a  
saturated aqueous NaHCO<sub>3</sub> solution, extracted with ethyl  
acetate, dried over anhydrous magnesium sulfate and  
25 filtered. The filtrates were concentrated under reduced  
pressure; the thus obtained residues were purified by  
column chromatography (silica gel) to give the titled  
compounds.

Examples conducted according to Scheme 12 are shown  
in Tables D-172 and D-173.

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Table D-172

## Example 172

(2S)-N-[(N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl)carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

5

Reaction1								
Compound T1 (g)	Compound 136 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	1.050	0.973	0.70	20.00	3	nHx:EA =1:1	I-a172	1.210
Reaction2								
Compound I-a172(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Product		Column sol.	
1.210	0.182	30.00	3		I-b172		MC:MeOH =20:1	
Reaction3								
Compound I-b172 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.744	1.170	1.050	0.72	20.00	52	nHx:EA =1:1	I-c172	0.518
Reaction4								
Compound I-c172(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.518	1.330	10.00	3	MC:MeOH =20:1		0.130	19.59	
ESI-MS(M <sup>+</sup> +1):527								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.42(8H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m),4.30 and 4.61(1H, m), 5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)								

Table D-173

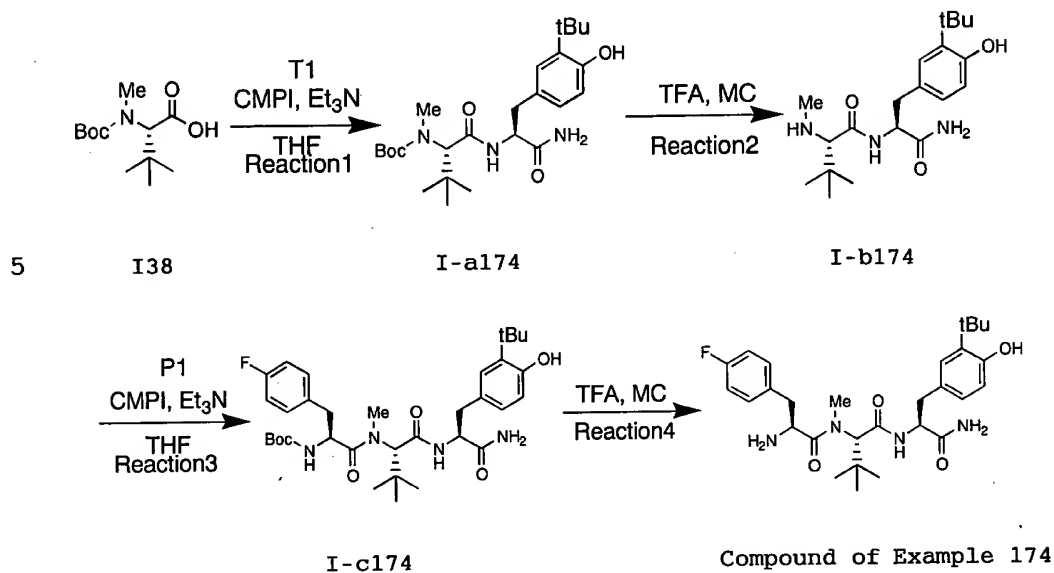
## Example 173

(2S)-N-[(N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl)carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

Reaction1								
Compound T1(g)	Compound I37 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.708	1.310	0.766	0.84	20.00	3	nHx:EA =1:1	I-a173	1.400
Reaction2								
Compound I-a173(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
1.400	0.210	30.00	3		I-b173		0.934	
Reaction3								
Compound I-b173 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.930	1.410	1.270	0.87	30.00	120	nHx:EA =1:1	I-c173	0.271
Reaction4								
Compound I-c173(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.271	0.700	5.00	3	MC:MeOH =20:1		0.030	24.76	
ESI-MS(M <sup>+</sup> +1):541								
1H-NMR(CDCI <sub>3</sub> ): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.50(10H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m), 4.30 and 4.61(1H, m),5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)								

Scheme 13 shows the synthesis process of Example 174.

Scheme 13: Synthesis scheme of Example 174



The synthesis process in scheme 13 is explained below.

#### Reaction step 1)

To a solution of Compound T1, Compound I38 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a174.

#### Reaction step 2)

To a solution of Compound I-a174 in dichloromethane, TFA was added under cooling and stirred at room temperature.

The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b174.

(Reaction step 3)

10 To a solution of Compound I-b174, Compound P1 and  
CMPI in THF, TEA was added under cooling and stirred at  
room temperature. The reaction mixture was mixed with  
water, extracted with ethyl acetate, washed with saturated  
brine, dried over anhydrous magnesium sulfate and filtered.  
15 The filtrate was concentrated under reduced pressure; the  
thus obtained residue was purified by column chromatography  
(silica gel) to give Compound I-c174.

(Reaction step 4)

To a solution of Compound I-c174 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Example conducted according to Scheme 13 is shown in  
Table D-174.

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Table D-174

## Example 174

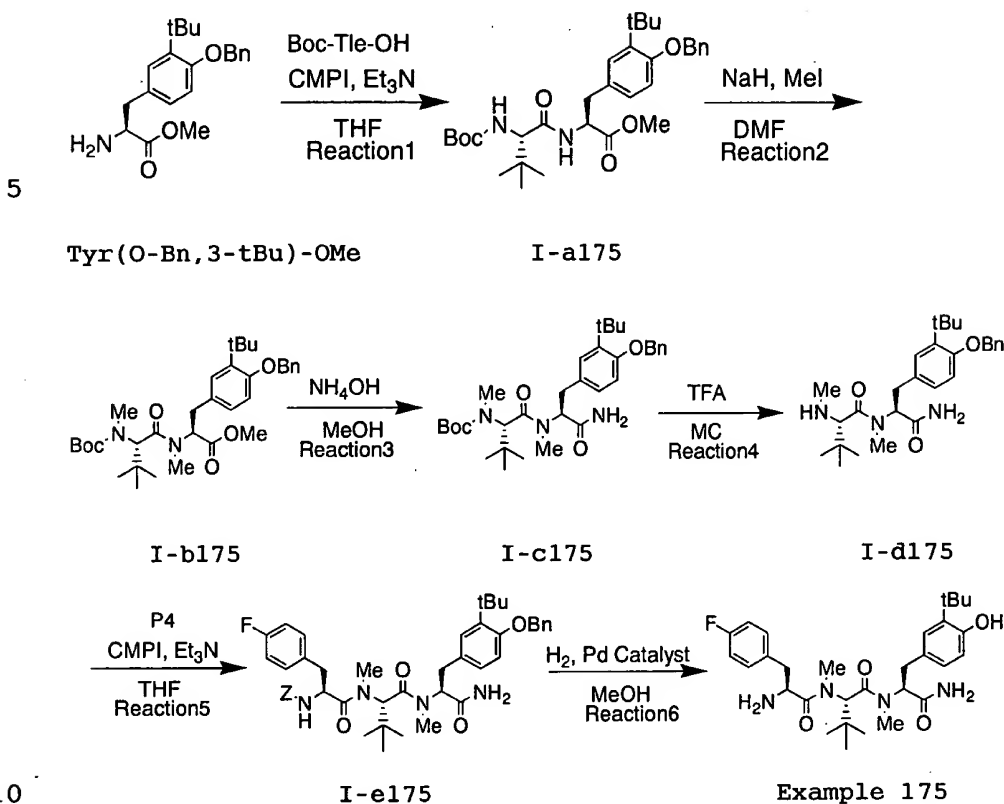
Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
Compound T1 (g)	Compound I38 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.633	0.660	0.756	0.37	15.00	24	nHx:EA =1:2	I-a174	0.670
Reaction2								
Compound I-a174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.670	2.00	10.00	1	MC:MeOH =10:1		I-b174	0.518	
Reaction3								
Compound I-b174(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.518	0.809	0.730	0.40	10.00	36	nHx:EA =1:2	I-c174	0.393
Reaction4								
Compound I-c174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.393	1.00	5.00	1	MC:MeOH =15:1		0.162	17.54	
ESI-MS(M <sup>+</sup> +1):529								
1H-NMR(CDC <sub>3</sub> ):(two rotamers) δ 1.02 and 1.03 (9H,s), 1.35 and 1.36(9H, s), 2.75(3H, s), 2.70 and 3.00(4H, m), 3.12(1H, dd, J=10.3, 6.3Hz), 3.60 and 3.82(1H, m), 4.64(1H, m), 5.50(1H, brs), 5.80 and 6.00(1H, brs), 6.70(1H, s), 6.80-7.15(6H, m)								



Scheme 14 shows the synthesis process of Example 175.

Scheme 14: Synthesis scheme of Example 175



The synthesis process in scheme 14 is explained below.

#### Reaction step 1)

15 To a solution of Tyr(O-Bn, 3-tBu)-OMe, Compound Boc-Tle-OH and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and

20 filtered. The filtrate was concentrated under reduced

pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a175.

Reaction step 2)

5           To a solution of Compound I-a175 in DMF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixture was mixed with water under cooling, neutralized by the addition of 1N HCl and extracted with EA/nHx (1/2). The organic layer was washed three times  
10 with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b175.

15   Reaction step 3)

          To a solution of Compound I-b175 in methanol, 28% aqueous ammonia was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate, washed with  
20 saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c175.

25   Reaction step 4)

          To a solution of Compound I-c175 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced

pressure, neutralized by the addition of a saturated aqueous  $\text{NaHCO}_3$  solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus  
 5 obtained residue was purified by column chromatography (silica gel) to give Compound I-d175.

Reaction step 5)

To a solution of Compound I-d175, Compound P4 and  
 10 CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the  
 15 thus obtained residue was purified by column chromatography (silica gel) to give Compound I-e175.

Reaction step 6)

To a solution of Compound I-e175 in methanol,  $\text{Pd}(\text{OH})_2$   
 20 was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the  $\text{Pd}(\text{OH})_2$ , the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

25 Example conducted according to Scheme 14 is shown in Table D-175.

Table D-175

Example 175

Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
Tyr(O-Bn,3-tBu)-OMe (g)	Boc-Tle-OH (g)	OMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.720	1.280	1.410	1.40	34.00	12	nHx:EA=5:1	I-a175	2.200
Reaction2								
Compound I-a175 (g)	NaH (g)	Methyl Iodide(ml)	DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.200	0.480	2.22	22.00	1	nHx:EA=5:1	I-b175	1.930	
Reaction3								
Compound I-b175 (g)	NH <sub>4</sub> OH (ml)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)		
1.930	130.00	230.00	20	nHx:EA=2:1	I-c175	0.564		
Reaction4								
Compound I-c175 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)		
0.680	2.78	8.00	1.5	MC:MeOH =20:1	I-d175	0.500		
Reaction5								
Compound I-d175 (g)	Compound P1(g)	OMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.951	0.546	0.50	12.50	12	nHx:EA=2:1	I-d175	0.254
Reaction6								
Compound I-d175 (g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.250	0.050	10.00	3	MC:MeOH=15:1	0.098	19.280		
ESI-MS(M <sup>+</sup> +1):543								
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): δ 0.80(9H, s), 1.37(9H, s), 2.68(1H, dd, J=13.6, 7.3Hz), 2.85-3.01(2H, m), 2.92(3H, s), 2.98(3H, s), 3.11-3.22(1H, m), 3.94(1H, t, J=7.0Hz), 5.19(1H, s), 5.22(1H, brs), 5.37(1H, dd, J=10.5, 5.6Hz), 5.98(1H, brs), 6.55(1H, d, J=7.9Hz), 6.88(1H, dd, J=8.0, 2.2Hz), 6.94-7.00(2H, m), 7.07-7.14(3H, m)								

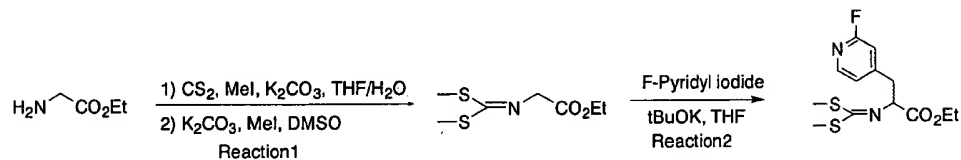


# Reference Example 27

## Synthesis of Intermediates P6-P8

The synthesis scheme is shown below.

### 5 Synthesis scheme of Intermediates P6-P8

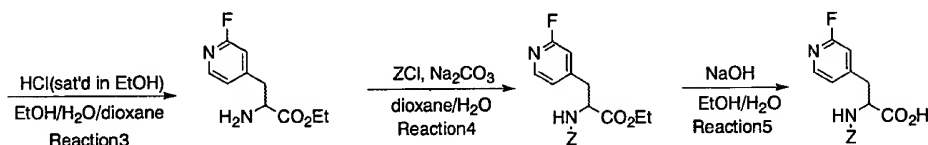


Glycine ethyl ester

I-a177-I

I-b177-I

hydrochloride



10

I-c177-I

I-d177-I

P6

The synthesis methods of Intermediates P6-P8 are explained below.

F-Pyridyl iodide [2-fluoro-4-(iodomethyl)pyridine and 2-fluoro-5-(iodomethyl)pyridine] were synthesized referring to J. Med. Chem., 1998, 41(23), 4615. P7 and P8 were synthesized according to a similar method of synthesizing P6 using the above 2-fluoro-5-(iodomethyl)pyridine and 4-(iodomethyl)-1-(trifluoromethyl)benzene.

20

Reaction step 1)

To a solution of glycine ethyl ester hydrochloride, CS<sub>2</sub> and water in THF, K<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>I were added dropwise and

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then stirred at room temperature. After the completion of the reaction, the reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The  
5 filtrate was concentrated under reduced pressure; to a solution of the thus obtained residue in a mixture of DMSO and water,  $K_2CO_3$  was added dropwise gradually and then under cooling with ice,  $CH_3I$  was added dropwise gradually, followed by stirring at room temperature. The reaction  
10 mixture was mixed with water, extracted with  $Et_2O$ , washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-  
15 al77-I.

Reaction step 2)

To a solution of Compound I-al77-I and t-BuOK in THF, F-pyridyl iodide was added dropwise gradually at  $-78^\circ C$   
20 while stirring. The reaction mixture was mixed with water, extracted with  $Et_2O$ , washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography  
25 (silica gel) to give Compound I-b177-I.

Reaction step 3)

To a solution of Compound I-b177-I in a mixture of





chromatography (silica gel) to give Intermediate P6.

The results are shown in Tables E-46 to E-48.

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Table E-46

Intermediate P6

3-(2-fluoro-4-pyridyl)-2-

[(phenylmethoxy)carbonylamino]propanoic acid

Reaction1-a							
Gly-OEt HCl(g)	K <sub>2</sub> CO <sub>3</sub> (g)	Methyl iodide(ml)	CS <sub>2</sub> (ml)	THF/H <sub>2</sub> O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate (g)	K <sub>2</sub> CO <sub>3</sub> (g)	Methyl iodide(ml)	DMSO/ H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA =5:1	I-a177-I	11.7000
Reaction2							
I-a177-I (g)	2-fluoro-4- (iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	2.520	1.190	32.00	2.50	nHx:EA =7:1	I-b177-I	2.480
Reaction3							
I-b177-I (g)	HCl(sat'd in EtOH) (ml)		EtOH/H <sub>2</sub> O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
2.480	11.50		11.50 / 11.50	6	16	I-c177-I	1.33
Reaction4							
I-c177-I (g)	ZCl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane/ H <sub>2</sub> O (ml)		Reaction time (hr)	Product	Amount (g)
1.330	0.99	1.000	18.00 / 18.00		2	I-d177-I	1.36
Reaction5							
I-d177-I (g)	NaOH (g)	EtOH/H <sub>2</sub> O (ml)		Reaction time (hr)		Amount (g)	
1.330	0.314	30.00 / 10.00		1.500		1.200	

Intermediate P7

3-(2-fluoro-5-pyridyl)-2-

[(phenylmethoxy)carbonylamino]propanoic acid

Reaction1-a							
Gly-OEt HCl(g)	K <sub>2</sub> CO <sub>3</sub> (g)	Methyl iodide(ml)	CS <sub>2</sub> (ml)	THF/H <sub>2</sub> O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate(g)	K <sub>2</sub> CO <sub>3</sub> (g)	Methyl iodide(ml)	DMSO/ H <sub>2</sub> O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA	l-a178-I	11.7000
Reaction2							
l-a178-I (g)	2-fluoro-5-(iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.990	8.37	2.380	60.00	3.00	nHx:EA	l-b178-I	4.300
Reaction3							
l-b178-I (g)	HCl(sat'd in EtOH)(ml)	EtOH/H <sub>2</sub> O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)	
4.300	20.00	12.00 / 12.00	10.00	16	l-c178-I	1.880	
Reaction4							
l-c178-I (g)	ZCl (ml)	Na <sub>2</sub> CO <sub>3</sub> (g)	Dioxane/ H <sub>2</sub> O (ml)	Reaction time (hr)	Product	Amount (g)	
1.880	1.40	1.410	25.00 / 25.00	2	l-d178-I	2.940	
Reaction5							
l-d178-I (g)	NaOH (g)	EtOH/H <sub>2</sub> O (ml)	Reaction time (hr)	Amount (g)			
2.620	0.606	40.00 / 10.00	1.500	2.400			

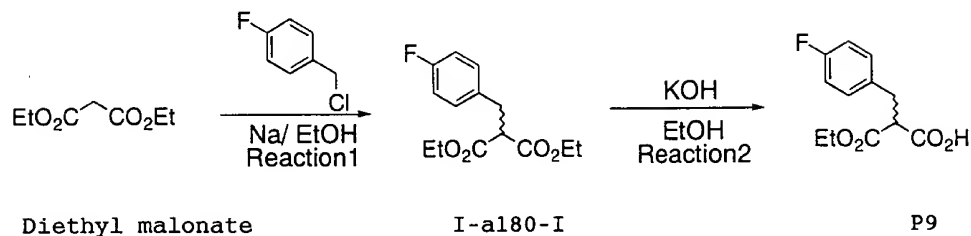
[illegible][illegible][illegible][illegible]

(Reference Example 28)

### Synthesis of Intermediate P9

The synthesis scheme is shown below.

#### 5 Synthesis scheme of Intermediate P9



The synthesis method of Intermediates P9 is explained below.

10

#### Reaction step 1)

To a solution of Na-metal in ethanol, diethyl malonate and 4-(chloromethyl)-1-fluorobenzene were added dropwise and then stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water, extracted with Et<sub>2</sub>O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give Compound I-a180-I in a crude form.

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#### Reaction step 2)

To a solution of Compound I-a180-I in ethanol, KOH was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water and washed with Et<sub>2</sub>O. The aqueous layer was

25

adjusted to a pH of 3-4 by the addition of 1N HCl,  
extracted with ethyl acetate, washed with saturated brine,  
dried over anhydrous magnesium sulfate and filtered. The  
filtrate was concentrated under reduced pressure; the thus  
5 obtained residue was purified by column chromatography  
(silica gel) to give Intermediate P9.

Result is shown in Table E-49.

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Table E-49

Intermediate P9

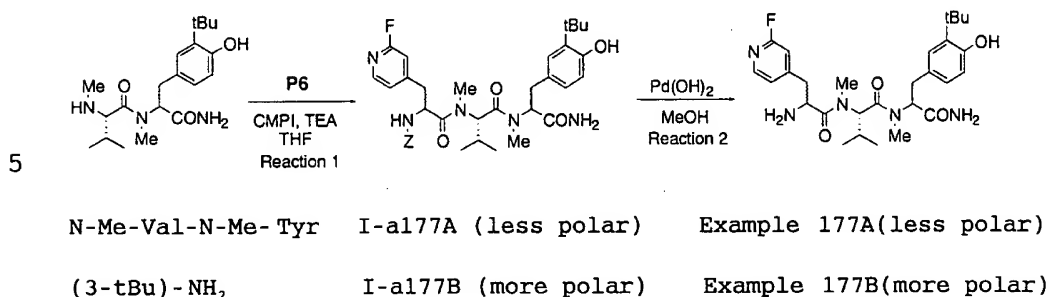
2-(Ethoxycarbonyl)-3-(4-fluorophenyl)propanoic acid

Reaction1					
Diethyl malonate (g)	4-(chloromethyl)-1- fluorobenzene (ml)	Na-metal (g)	EtOH (ml)	Product	Amount (g)
15.000	10.90	2.180	120.00	I-a180-I	25.000
Reaction2					
I-a180-I (g)	KOH (g)	EtOH (ml)	Amount (g)		
2.160	5.170	160.00	1.400		

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The synthesis scheme of Examples 177A to 179B is shown in Scheme 15.

Scheme 15: Synthesis scheme of Examples 177A to 179B



Referring to Examples 177A and 177B, the synthesis process of Scheme 15 is explained below:

10

#### Reaction step 1)

To a solution of Compound P6, N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a177A (less polar) and Compound I-a177B (more polar).

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#### Reaction step 2)

To solutions of Compound I-a177A (less polar) and Compound I-a177B (more polar) in methanol, Pd(OH)<sub>2</sub> was added and stirred in a hydrogen atmosphere at room

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temperature. After filtering off the  $\text{Pd}(\text{OH})_2$ , the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

5

Example 178 (178A and 178B) and Example 179 (179A and 179B) were conducted similar to the above, except that P7 and P8 were employed, respectively, instead of P6.

10           Examples conducted according to Scheme 15 are shown in Tables D-177A to D-179B.

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Table D-177A

Example 177A:Less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
ethyl)-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoyle  
5 amino]-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Compound P6(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.776	0.886	0.711	0.45	30.00	16	nHx:EA=1:1	I-a177A	0.275
							I-a177B	0.288
Reaction2								
Compound I-a177A(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.275	0.042	20.00	3	MC:MeOH =20:1	0.160	17.50		
ESI-MS(M <sup>+</sup> +1):530								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.32, 0.42 and 0.60, 0.88(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.20(1H, m), 2.52 and 2.91, 2.95(6H, s), 2.60-3.28(4H, m), 2.95(3H, s), 3.75(1/2H, dd, J=8.8, 6.1Hz), 3.95(1/2H, t, J=8.8Hz), 4.65 and 5.00(1H, d, J=8.8Hz), 4.96 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.60 and 6.05(1H, brs), 6.60 and 6.15(1H, d, J=8.8Hz), 6.70 and 7.04(2H, m), 6.92 and 7.12(2H, m), 8.12(1H, m)								

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Table D-177B

Example 177B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
lethyl)-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoyl  
5 amino]-3-methyl-N-methylbutanamide

Reaction2						
Compound l-a177B(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.288	0.043	20.00	3	MC:MeOH =20:1	0.160	15.48
ESI-MS(M <sup>+</sup> +1):530						
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.46, 0.72 and 0.78, 0.91(6H, d, J=7.1-7.9Hz), 1.32 and 1.38(9H, s), 2.15-2.40(1H, m), 2.50, 2.83, and 3.0, 3.08(6H, s), 2.40-3.40(5H, m), 3.70 and 3.90(1H, dd, J=8.8, 3.5-4.4Hz), 4.81 and 5.05(1H, d, J=9.7Hz), 4.99 and 5.52(2H, m), 6.05 and 6.49(1H, brs), 6.48 and 6.64(1H, d, J=7.9Hz), 6.74 and 6.76, 6.82(2H, brs), 6.90-7.18(2H, m), 8.12(1H, d, J=6.2Hz)						

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Table D-178A

Example 178A:less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
 lethyl)-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoyl  
 5 amino]-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Compound P7(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.140	0.917	0.58	20.00	3	nHex:EA=1:1	I-a178A	0.380
							I-a178B	0.100

Reaction2						
Compound I-a178A(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.380	0.057	10.00	3	MC:MeOH =20:1	0.210	17.76

ESI-MS(M<sup>+</sup>+1):530

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.32, 0.42 and 0.60, 0.89(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.30(1H, m), 2.50, 2.90 and 2.94, 2.95(6H, s), 2.58-3.29(4H, m), 3.70(1/2H, dd, J=8.8, 6.1Hz), 3.90(1/2H, t, J=8.8Hz), 4.67 and 5.04(1H, d, J=8.8Hz), 4.95 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.70(1H, brs), 6.05 and 6.55(1H, brs), 6.58 and 6.65(1H, d, J=8.8Hz), 6.75-6.99(2H, m), 7.10 and 7.18(1H, brs), 7.58-7.75(1H, m), 8.12(1H, m)

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Table D-178B

Example 178B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
 lethyl)-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoyl  
 5 amino]-3-methyl-N-methylbutanamide

Reaction2						
Compound l-a178B(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.100	0.015	5.00	3	MC:MeOH =20:1	0.040	15.65
ESI-MS(M <sup>+</sup> +1):530						
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.50, 0.75 and 0.77, 0.95(6H, d, J=7.1-7.9Hz), 1.32 and 1.39(9H, s), 2.00-2.30(1H, m), 2.47, 2.83 and 3.0, 3.05(6H, s), 2.18-3.42(4H, m), 3.61 and 3.82(1H, dd, J=8.8, 3.5-4.0Hz), 4.85 and 5.07(1H, d, J=9.7Hz), 5.57 and 5.70, 5.79, 6.11(2H, m and brs), 6.55 and 6.65(1H, d, J=7.9-8.8Hz), 6.73, 6.88 and 6.97(2H, m), 7.13(1H, brs), 7.60-7.75(1H, m), 7.97 and 8.05(1H, brs)						

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 Total 6222860

Table D-179A

Example 179A:less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
 ethyl)-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]pr  
 5 opanoylamino}-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Compound P8(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.626	0.435	0.3	30.00	3	nHx:EA=1:1	I-a179A	0.330
							I-a179B	0.332

Reaction2						
Compound I-a179A(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.330	0.049	10.00	3	MC:MeOH=20:1	0.136	19.89

ESI-MS(M<sup>+</sup>+1):579

<sup>1</sup>H-NMR(CDC<sub>3</sub>): (two rotamers) δ 0.49, 0.74 and 0.79, 0.93(6H, d, J=6.3-6.8Hz), 1.34 and 1.39(9H, s), 2.25-2.48(1H, m), 2.53, 2.79 and 3.01, 3.05(6H, s), 2.58-3.40(4H, m), 3.74 and 3.90(1H, m), 4.87 and 5.07(1H, d, J=10.5-10.9Hz), 5.38-5.10(2H, m), 6.20(2/3H, brs), 6.40 and 6.65(1H, d, J=7.9Hz), 6.58(1/3H, brs), 6.73 and 6.97(1H, d, J=7.9-8.4Hz), 7.12(1H, m), 7.27-7.30(2H, m), 7.55-7.60(2H, m)

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Table D-179B

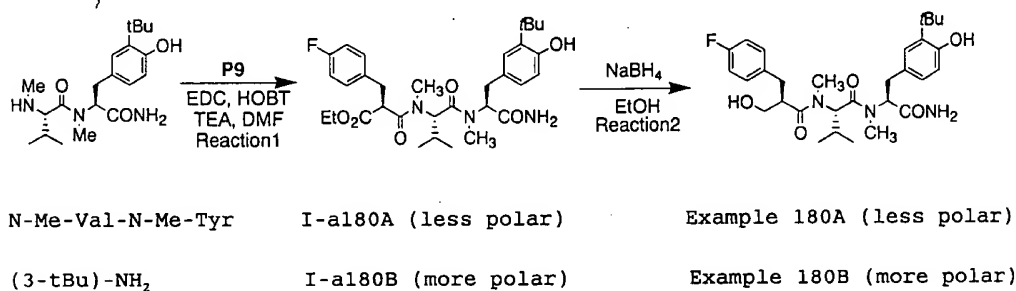
Example 179B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl-ethyl)-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino}-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a179B(g)	Pd(OH) <sub>2</sub> (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.332	0.049	10.00	3	MC:MeOH =20:1	0.123	22.09
ESI-MS(M <sup>+</sup> +1):579						
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.33, 0.36 and 0.55, 0.87(6H, d, J=6.4-6.9Hz), 1.37 and 1.41(9H, s), 2.00-2.20(1H, m), 2.56, 2.92 and 2.98(6H, s), 2.60-3.21(4H, m), 3.77 and 3.96(1H, m), 4.67 and 5.02(1H, d, J=10.6-10.9Hz), 4.96 and 5.45(1H, dd, J=9.0-11.3, 3.4-6.0Hz), 5.67 and 6.04(1H, brs), 6.57 and 6.63(1H, d, J=7.9Hz), 6.74 and 6.94(1H, dd, J=8.0-9.8, 1.8-2.1Hz), 7.08 and 7.16(1H, d, J=1.9Hz), 7.27-7.37(2H, m), 7.52-7.60(2H, m)						

Scheme 16 shows synthesis process of Examples 180A and B.

10 Scheme 16: synthesis process of Examples 180A and B



The synthesis process of Scheme 16 is explained below.

Reaction step 1)

To a solution of Compound P9, N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>, EDCL and HOBT in DMF, TEA was added under

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cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with Et<sub>2</sub>O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel) to give Compound I-a180A (less polar) and Compound I-a180B (more polar).

Reaction step 2)

10 To the solutions of Compound I-a180A (less polar) and Compound I-a180B (more polar) in ethanol, NaBH<sub>4</sub> was added under cooling and stirred at room temperature. The reaction mixtures were mixed with a 1N HCl solution, extracted with Et<sub>2</sub>O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds (less polar compound and more polar compound).

20 Tables D-180A and B show Examples conducted according to Scheme 16.



Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	1500	500	1000	2500
Health status	0.5	0.5	0	1
Smoking status	0.5	0.5	0	1
Alcohol consumption	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1
Depression score	0.5	0.5	0	1
Loneliness score	0.5	0.5	0	1
Quality of life score	0.5	0.5	0	1
Overall health score	0.5	0.5	0	1

5 panoylamino}-3-methyl-N-methylbutanamide

5 panoylamino}-3-methyl-N-methylbutanamide

Reaction1									
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Compound P9(g)	EDCl (g)	HOBt (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	1.29	1.030	0.824	1.08	30.00	2.5	nHc:EA=1:1	I-a180A	0.700
								I-a180B	0.820

Reaction2						
Compound I-a180A(g)	NaBH <sub>4</sub> (g)	EtOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.700	0.490	30.00	3	MC:MeOH=20:1	0.17	21.83

ESI-MS(M<sup>+</sup>+1):544

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.48, 0.74 and 0.76, 0.92(6H, d, J=6.0-7.2Hz), 1.35 and 1.39(9H, s), 2.05-2.50(1H, m), 2.50, 2.80 and 2.98, 3.01(6H, s), 2.40-3.36(5H, m), 3.50-3.70(2H, m), 3.50-3.70(2H, m), 4.90 and 5.08(1H, d, J=10.6Hz), 5.45(1H, m), 5.50 and 6.05(1H, brs), 5.70 and 6.20(1H, brs), 6.44 and 6.64(1H, d, J=8.8-8.3Hz), 6.73-7.15(7H, m)

Table D-180B

Example 180B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl  
lethyl)-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpro  
panoylamino}-3-methyl-N-methylbutanamide

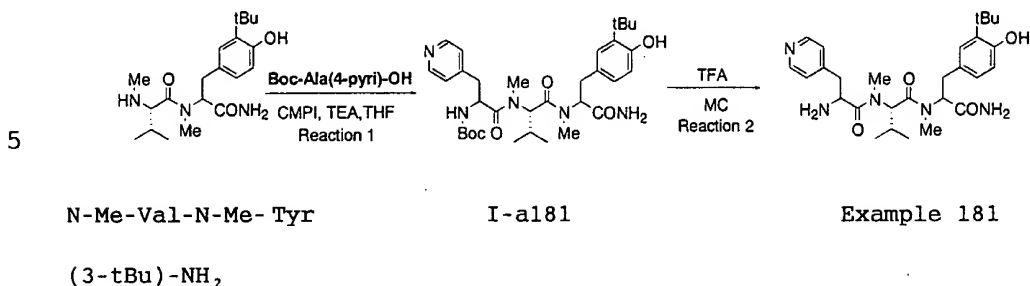
5

Reaction2						
Compound I-a180B(g)	NaBH <sub>4</sub> (g)	EtOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.820	0.492	30.00	3	MC:MeOH =20:1	0.060	23.95
ESI-MS(M <sup>+</sup> +1):544						
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.17-0.20 and 0.44, 0.84(6H, m and d, J=6.5-6.7Hz), 1.36 and 1.40(9H, s), 2.00-2.20(1H, m), 2.41 and 2.90, 2.92(6H, s), 2.67-4.00(13H, m), 4.73 and 5.00(1H, d, J=10.5Hz), 5.20 and 5.35(1H, m), 5.83 and 6.18(1H, brs), 6.38 and 6.51(1H, brs), 6.62 and 6.65(1H, d, J=7.9Hz), 6.75-7.20(8H, m)						

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The synthesis scheme of Examples 181 and 182 is shown in Scheme 17.

Scheme 17: Synthesis scheme of Examples 181 and 182



Referring to Example 181, the synthesis process of Scheme 17 is explained below:

Reaction step 1)

To a solution of Compound Boc-Ala(β-4-pyridyl)-OH, N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a181.

Reaction step 2)

To a solution of Compound I-a181 in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under

reduced pressure, extracted with dichloromethane, washed  
with saturated brine, dried over anhydrous magnesium  
sulfate and filtered. The filtrate was concentrated under  
reduced pressure; the thus obtained residue was purified  
5 by column chromatography (silica gel) to give the titled  
compound.

Compound of Example 182 was obtained according to a  
similar process to Example 181 using Boc-Ala( $\beta$ -4-pyridyl)-  
10 OH.

Examples conducted according to Scheme 17 are shown  
in Tables D-181 and D-182.

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$$\text{Ala}(\beta\text{-4-pyridyl})\text{-N-Me-Val-N-Me-Tyr(3-tBu)-NH}_2$$

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Boc-Ala(beta-4-pyridyl)-OH (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.680	0.500	0.960	0.52	15.00	24	MC:MeOH =30:1	I-a181	0.800

Reaction2						
Compound I-a181(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.800	4.00	20.00	3	MC:MeOH =20:1	0.450	13.30

ESI-MS(M <sup>+</sup> +1):512
<sup>1</sup> H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.40, 0.72 and 0.82, 0.96(6H, d, J=6.3-6.7Hz), 1.37 and 1.42(9H, s), 2.05-2.30(1H, m), 2.51, 2.89 and 2.94, 2.96(6H, s), 2.59-3.30(4H, m), 4.65-5.05(1H, m), 5.30(1H, s), 5.45-5.05(1H, m), 6.30-6.45(1H, m), 6.60-7.05(2H, m), 7.10-7.20(2H, m), 8.20-8.25(2H, m)

Table D-182

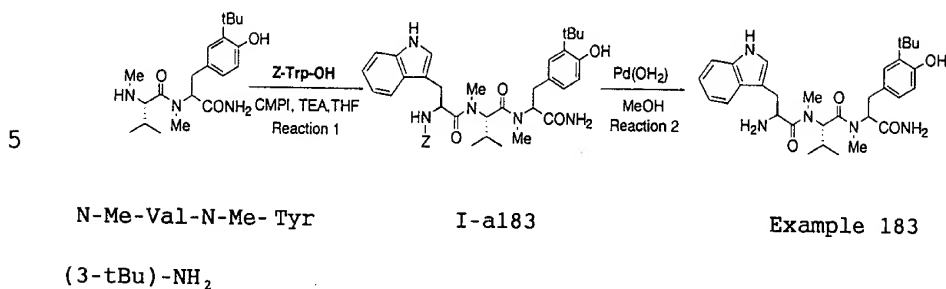
## Example 182

Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Boc-Phe(4-CN)-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.500	0.660	0.48	15.00	24	MCMeOH =30:1	I-a182	0.900
Reaction2								
Compound I-a182(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.900	4.00	20.00	4	MCMeOH =20:1	0.520	16.82		
ESI-MS(M <sup>+</sup> +1):536								
1H-NMR(CDCl <sub>3</sub> ): (two rotamers) δ 0.48, 0.76 and 0.85, 0.94(6H, d, J=6.3-6.8Hz), 1.37 and 1.43(9H, s), 2.20-2.70(1H, m), 2.55, 2.85 and 2.95, 3.05(6H, s), 3.15-3.40(2H, m), 3.65-3.85(2H, m), 4.75-5.20(2H, m), 5.40-5.50(1H, m), 6.40-6.65(1H, m), 6.75-6.85(1H, m), 6.95-7.15(1H, m), 7.25-7.35(2H, m), 7.58-7.63(2H, m)								

The synthesis scheme of Example 183 is shown in Scheme 18.

Scheme 18: Synthesis scheme of Example 183



The synthesis process of Scheme 18 is explained below:

10 Reaction step 1)

To a solution of Z-Trp-OH, N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub> and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a183.

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Reaction step 2)

To a solution of Compound I-a183 in methanol, Pd(OH)<sub>2</sub> was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd(OH)<sub>2</sub>, the filtrate was concentrated under reduced pressure; the thus

obtained residue was purified by column chromatography  
(silica gel) to give the titled compound.

Example conducted according to Scheme 18 is shown in  
Table D-183.

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Table D-183

## Example 183

Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH<sub>2</sub>

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH <sub>2</sub> (g)	Z-Trp-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.700	0.660	0.48	15.00	24	MC:MeOH =30:1	I-a183	0.700

Reaction2						
Compound I-a183(g)	Pd(OH) <sub>2</sub>	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.700	0.100	20.00	24	MC:MeOH =20:1	0.380	18.14

ESI-MS(M<sup>+</sup>+1):550

<sup>1</sup>H-NMR(CDCl<sub>3</sub>): (two rotamers) δ 0.39, 0.73 and 0.79, 0.93(6H, d, J=6.3-6.7Hz), 1.33 and 1.39(9H, s), 2.15-2.35(2H, m), 2.37, 2.75 and 2.95, 3.05(6H, s), 2.60-3.15(2H, m), 3.25-3.40(2H, m), 3.80-4.05(1H, m), 4.70-5.10(1H, m), 6.30-6.55(1H, m), 6.65-7.20(5H, m), 7.40-7.60(2H, m)

Test Example 1

Motilin receptor binding test

5 A motilin receptor binding test was conducted in the following manner [Vantrappen et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered rabbit, had the mucous membrane separated and homogenized in 50 mM Tris buffer to prepare a protein sample. The protein sample was incubated together with <sup>125</sup>I motilin 25 pM and thereafter the radioactivity bound to the protein was measured. Specific binding was defined as the difference between the radioactivity in the case of adding a great excess amount of motilin (10<sup>-7</sup> M) and that in the case of no adding. The activity of the compound was expressed by IC<sub>50</sub> (in nM), as the concentration sufficient to reduce the specific binding by 50%. Result is shown in Tables F-1 to F-3.

Test Example 2

20 Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit was investigated by the following method. A duodenum specimen (5 x 15 mm) extracted from a slaughtered rabbit was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was filled with a Krebs solution kept at 28°C. A mixed gas (95% O<sub>2</sub> and 5% CO<sub>2</sub>) was continuously bubbled into the Krebs

solution and the contraction of the duodenum specimen was recorded isotonically (with a 1-g load) via an isotonic transducer (ME-3407, ME Commercial, Tokyo, Japan). The degree of contraction was expressed in relative values, 5 with the contraction by acetylcholine at a dose of  $10^{-4}$  M being taken as 100%. The activity of the compound was calculated as  $pA_2$  value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The result is shown in Tables F-1 to F-3.

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Table F-1

Example No.	Motilin receptor binding test, $IC_{50}$ (nM)	Contraction suppressing test, $pA_2$
1	0.89	8.8
2	0.71	8.7
3	1.5	8.7
4	1.6	8.3
8	0.35	9.5
9	1.0	9.0
12	0.52	9.3
14	0.70	9.3
15	0.82	8.5
16	0.41	9.4
17	0.70	9.1
19	2.2	8.7
21	0.27	9.8
22	0.52	8.3
23	0.67	9.3
24	0.94	9.1

Table F-2

Example No.	Motilin receptor binding test, IC <sub>50</sub> (nM)	Contraction suppressing test, pA <sub>2</sub>
26	7.3	8.0
27	1.2	8.6
28	0.52	9.0
29	0.45	8.7
30	0.81	9.1
31	0.79	9.5
32	0.76	9.1
33	1.7	8.4
34	1.5	9.4
35	1.7	8.8
36	2.3	8.8
37	0.60	8.8
38	3.0	8.2
39	2.0	8.7
40	1.6	8.6
41	3.1	8.4
42	1.2	8.3
43	1.9	8.5
44	3.6	8.5
63	0.62	8.4
64	1.0	9.0
101	0.24	8.9
102	0.31	9.0
103	0.86	8.9

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Table F-3

Example No.	Motilin receptor binding test, $IC_{50}$ (nM)	Contraction suppressing test, $pA_2$
104	0.32	9.1
105	0.31	9.8
106	0.62	9.8
107	0.39	8.7
108	0.43	9.0
109	0.17	8.7
119	0.40	9.4
120	0.27	9.0
121	0.41	8.9
122	0.47	9.0
123	0.70	9.1
124	0.98	9.1
125	1.0	9.0
126	1.9	9.2
127	1.7	8.7
128	1.5	8.7
129	4.0	8.5
132	0.86	8.9

Table F-4

Example No.	Motilin receptor binding test, IC <sub>50</sub> (nM)	Contraction suppressing test, pA <sub>2</sub>
133	1.1	8.2
134	1.5	8.3
135	0.70	8.5
136	6.8	7.6
140	4.0	8.2
142	0.62	8.6
144	2.0	8.5
148	4.1	8.4
151	0.36	8.2
155	2.5	8.1
157	6.1	8.1
163	2.4	7.8
165	2.8	8.2
166	1.8	9.8
182	2.3	8.5
183	0.57	9.5

#### INDUSTRIAL APPLICABILITY

- 5 The compounds of the present invention function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.